

*REMARKS/ARGUMENTS**The Present Invention and the Pending Claims*

Claims 1-24 are pending. Claims 1-6 and 13-18 are directed to a method for producing a mixture of 5 $\alpha$ -pregnane derivatives of formulae (II) and (III). Claims 7-12 and 19-24 are directed to a method for producing a mixture of (20S)-7 $\alpha$ ,21-dihydroxy-20-methyl-5 $\alpha$ -pregn-3-one of formula (VI) and (20S)-7 $\alpha$ ,21-dihydroxy-20-methyl-5 $\alpha$ -pregn-1-en-3-one of formula (VII).

*Summary of the Claim Amendments*

Claims 1 and 7 have been amended to recite that the metal is present in an amount of 1.6 to 5 molar equivalents relative to the compound represented by the formula (I). This amendment is supported by the specification at, for example, page 14, lines 31, through page 15, line 5. No new matter has been added by way of these amendments.

*Summary of the Office Action*

Claims 1-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 1-24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

Claims 1-24 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nakazawa et al. (U.S. Patent Application Publication 2003/0181742) in combination with Moriarty et al. (*Tetrahedron Letters*, 35(44): 8103-8106 (1994)).

Reconsideration of the pending claims is hereby requested.

*Discussion of the Indefiniteness and Written Description Rejections*

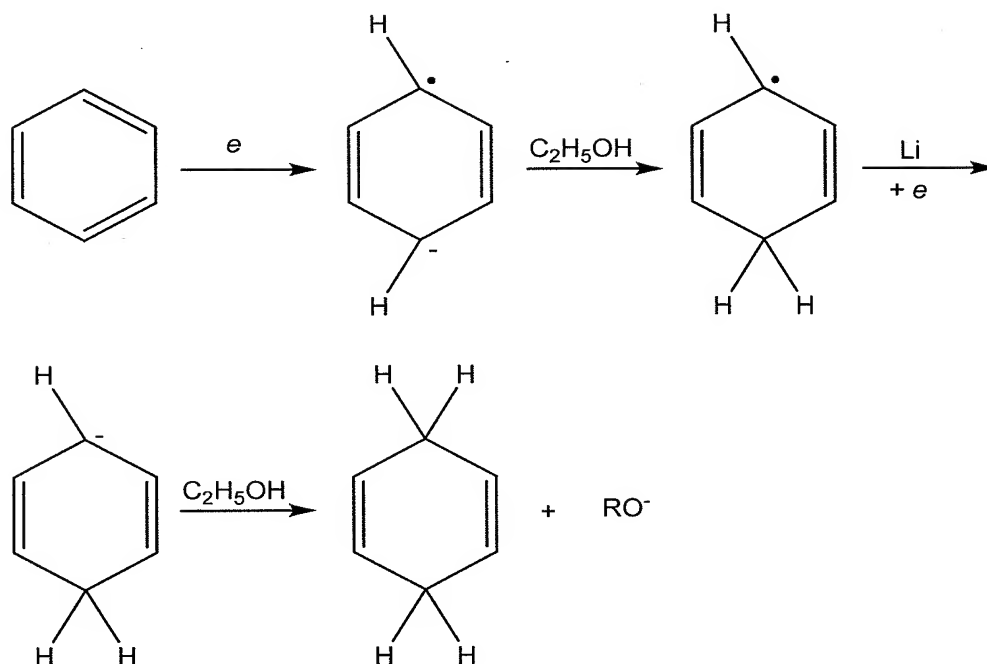
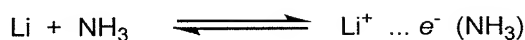
Claims 1-24 allegedly are indefinite. The Office contends that the phrase "wherein the metal is present in an amount of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by the formula

(I)” is unclear because the quantities of the metal and compound of formula (I) are not recited. Without specifying the amount of the metal and compound of formula (I), the Office contends that it is not possible to determine the metes and bounds of the claims.

Claims 1-24 allegedly lack written description. According to the Office Action, the amount of metal necessary to reduce the carbon-carbon double bond of the compound of formula (I) is not disclosed in the specification or otherwise readily determined. As a basis of the rejection, the Office points out that the working example in the application describe a 4.23 molar excess (Example 1) of metal relative to the compound of formula (I). The Office contends that one cannot discern whether this amount falls within the claimed range, and, as such, the specification lacks a written description of the claimed amount of metal (“wherein the metal is present in an amount of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by the formula (I)”).

As discussed above, claims 1 and 7 have been amended to recite that the metal is present in an amount of 1.6 to 5 molar equivalents relative to the compound represented by the formula (I).

As illustrated in the Birch reduction mechanism, as described in the reference Bansal, R. K., *Synthetic Approaches in Organic Chemistry*, Hyde, C. W., Ed. (Jones and Bartlett: London, 1996), pages 113-114 (copy enclosed), it is well known that the theoretically required amount of the metal (electron source) in a Birch reduction is two molar equivalents per one carbon-carbon double bond.



Therefore, one skilled in the art can easily understand that “the amount necessary for reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by formula (I)” is 2 molar equivalents relative to the compound of formula (I).

In Example 1, the amount of lithium (46.1 mmol) is 4.22 molar equivalents ( $2 \times 2.11 = 4.22$ ) relative to (20S)-21-tert-butyldimethylsilyloxy-7 $\alpha$ -hydroxy-20-methylpregna-1,4-dien-3-one (10.9 mmol). Since, as explained above, 2.0 molar equivalents are needed in such a situation to reduce the single carbon-carbon double bond of the compound, the actual amount of metal utilized in Example 1 is 2.11 times the amount necessary for reducing the 4,5-double bond in the compound of formula (I). The value of 2.11 falls within the range of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond at the 4,5-positions of the compound represented by formula (I).

Claims 1 and 7 previously were amended to recite that the metal is present in an amount of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond at the C<sub>4</sub>-C<sub>5</sub>-positions of the compound represented by the formula (I) (specification at, e.g., page 14, lines 31, through page 15, line 5). To clarify the amount of metal relative to the

amount of the compound of formula (I), the range 0.8 to 2.5 has been amended to read molar equivalents. The following table describes the calculation underlying the amendment of the range of 0.8 to 2.5 times to a range of molar equivalents.

molar equivalents of metal relative to the compound of formula (I) required	metal range: 0.8 to 2.5 times
2	1.6 to 5 times (0.8x2) to (2.5x2)

Thus, it is clear that the specification discloses the claimed range (i.e., 1.6 to 5 molar equivalents of metal relative to the compound of formula (I)) both generally and specifically (see, e.g., specification at page 14, lines 31, through page 15, line 5 and Example 1). Moreover, the amended claims more clearly recite the amount of metal to be added, since the recited ranges are in molar equivalents of the metal relative to the compound of formula (I). There is no doubt that one of ordinary skill in the art would be able to discern the quantities of both the metal and compound of formula (I) to be used in the context of the claimed invention as defined by the pending claims.

In view of the foregoing, Applicants submit that the amended claims are clear and definite and fully supported by the specification. As a result, Applicants respectfully request that the indefiniteness and written description rejections be withdrawn.

#### *Discussion of the Obviousness Rejection*

Claims 1-24 allegedly are obvious over Nakazawa et al. in combination with Moriarty et al. The reasons for the obviousness rejection are the same as provided in the previous Office Action.

Applicants traverse this rejection based on the following discussion.

As previously discussed, claims 1-24 are directed to a method for producing *a mixture* of 5 $\alpha$ -pregnane derivatives (i.e., mixtures of either compounds of formulae (II) and (III) (claims 1-6 and 13-18) or formulae (VI) and (VII) (claims 7-12 and 19-24)). As discovered

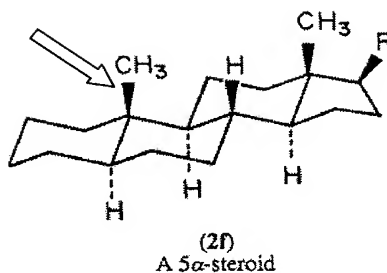
by Applicants, obtaining a *mixture* of the ketone compound and the en-one compound is directly related to the amount of the reducing reagent used in the reaction.

In contrast, the claimed mixture is *not* ultimately obtained in the reaction of Nakazawa et al. because only the ketone compound (i.e., a compound of formula (II) or (VI)) is produced (paragraph 0105, Example 1). In response, the Office states, "because the C<sub>4</sub>-C<sub>5</sub> double bond is less sterically hindered and more susceptible to reduction, it would be expected to be reduced first, in the initial phase of the reaction" (Office Action, page 5, first paragraph). As a result of this alleged steric hindrance, the Office asserts that the claimed mixture of the ketone compound and the en-one compound inherently would be formed in the method of Nakazawa et al. (Office Action, top of page 5, through top of page 6).

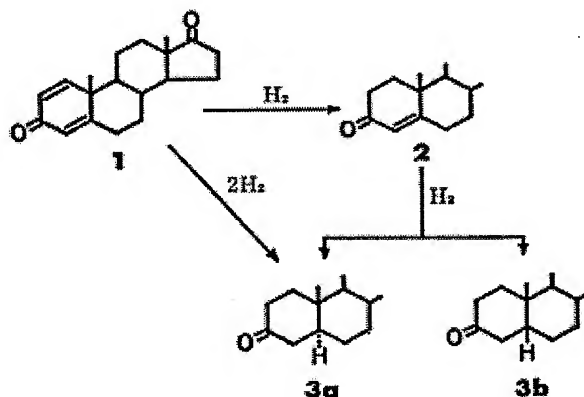
In support of the en-one compound formation (i.e., a compound of formula (III) or (VII)) in Nakazawa et al., the Office contends that it would be expected for the C<sub>4</sub>-C<sub>5</sub> double bond to be more easily reduced because the C<sub>1</sub>-C<sub>2</sub> double bond is sterically hindered by the C<sub>10</sub> methyl group (Office Action, page 4, bottom paragraph). This contention set forth by the Office, however, is based solely on conjecture and is not supported by the scientific literature.

As illustrated in the mechanism of the Birch reduction, shown above and described in Bansal, R. K. (*Synthetic Approaches in Organic Chemistry*, Hyde, C. W., Ed. (Jones and Bartlett: London, 1996), pages 113-114), the reducing species for a Birch reduction is an electron (e<sup>-</sup>). An electron (e<sup>-</sup>) has the smallest size in the field of organic chemistry, and as a result, an electron as a reducing species inherently is not susceptible to steric hindrance. Because steric hindrance does not play a role in the reduction, it does not factor into the selectivity of the reducing step (e.g., C<sub>4</sub>-C<sub>5</sub> double bond versus C<sub>1</sub>-C<sub>2</sub> double bond).

In addition, as shown in the compound of formula (2f), shown below and on page 1787 of Moss, G. P. ("Nomenclature of Steroids (Recommendation of 1989)," *Pure & Appl. Chem.*, 61(10): 1783-1822 (1989); copy enclosed), the C<sub>10</sub> methyl group is axially configured toward the  $\beta$ -face of the steroid skeleton. Therefore, any reaction species (e.g., an electron) could readily access the C<sub>1</sub>-C<sub>2</sub> double bond from the  $\alpha$ -face.



Furthermore, Nishimura et al. (*Bulletin of the Chemical Society of Japan*, 48(10): 2852-2854 (1975); copy enclosed) discloses the selective homogenous hydrogenation of 1,4-androstadiene-2,17-dione (**1**), which has a C<sub>10</sub> methyl group, using dichlorotris(triphenylphosphine)ruthenium as a catalyst. The reducing species is considered to be a dichlorotris(triphenylphosphine)ruthenium hydrido complex, which is much larger in size as compared to an electron (see Nishimura et al., page 2853, right column, lines 6-10). As shown in Nishimuri et al., the C<sub>1</sub>-C<sub>2</sub> double bond of compound **1**, which the Office regards as more sterically hindered than the C<sub>4</sub>-C<sub>5</sub> double bond, is reduced *first* by the reducing species to give 4-androstene-3,17-diene (**2**) (see Nishimura et al., page 2852, left column, reaction scheme).



Nishimura et al. suggests that the reducing species adds to compound **1** from the  $\alpha$ -face (see Nishimura et al., page 2853, right column, lines 6-12). Therefore, even when a reducing species is used with such a relatively large steric size, the attack from the  $\alpha$ -face is considered to be unaffected by the steric hindrance of the C<sub>10</sub> methyl group.

Consequently, Applicants maintain that the Office's contention that the C<sub>4</sub>-C<sub>5</sub> double bond would be expected to be more easily reduced than the C<sub>1</sub>-C<sub>2</sub> double bond because of steric hindrance by the C<sub>10</sub> methyl group is technically incorrect.

Instead, based on the foregoing evidence, it is apparent that the reduction selectivity of the C<sub>1</sub>-C<sub>2</sub> double bond versus the C<sub>4</sub>-C<sub>5</sub> double bond varies and depends on the reducing species. Contrary to the Office's contention, the C<sub>10</sub> methyl group does not influence the reaction. Accordingly, Applicants maintain that it is not obvious for one of ordinary skill in the art to predict the selectivity of the present invention. Because the selectivity is not predictable, it cannot be argued that Nakazawa et al. inherently discloses the claimed process, as defined by the pending claims.

Claims 1 and 7 have been amended to recite that the metal is present in an amount of 1.6 to 5 molar equivalents relative to the compound represented by the formula (I). Example 1 of Nakazawa et al. discloses using 10 molar equivalents of lithium (58.1 mmol) relative to (20S)-7 $\alpha$ ,21-dihydroxy-20-methyl-pregna-1,4-dien-3-one (5.81 mmol). Not only is this amount of metal well *outside* the claimed range of 1.6 to 5 molar equivalents, the large excess of metal used in Nakazawa et al. (10 molar equivalents) ensures that the intermediate en-one compound (i.e., a compound of formula (III) or (VII)) is *not* ultimately produced, as required by the pending claims.

Because Nakazawa et al. does not disclose protecting the hydroxyl group(s) prior to a reduction step, as required by the pending claims, the Office relies on Moriarty et al.'s disclosure of protecting a 24-hydroxyl group. Compound 5 of Moriarty et al., which is subjected to the Birch reduction, does not have a 7-hydroxyl group, as alleged by the Office, but rather has a 7-oxo group. Applicants maintain that Moriarty et al. describes (i) a Birch reduction that does not necessarily require a hydroxyl-protecting group and (ii) other reactions that must include a hydroxyl-protecting group (e.g., the reduction using K-selectride, and the Oppenauer oxidation). As a result, the 24-hydroxyl group in Moriarty et al. has been protected because of reaction steps other than the Birch reduction.

In response, the Office contends that one of ordinary skill in the art would have had a reasonable expectation of success that a Birch reduction could proceed in the presence of a TBDMS protecting group, regardless of the reasons why Moriarty et al. introduced the

protecting group (Office Action, page 6, second full paragraph). Applicants agree that one of ordinary skill in the art would understand that a Birch reduction could proceed in the presence of a TBDMS protecting group, but Applicants maintain that the question is whether that same artisan would have been directed by Moriarty et al. to protect a hydroxyl group (e.g., at the 21- and/or 24-position) prior to a Birch reduction. It is Applicants' contention that Moriarty et al. does not provide a credible reason to lead one of ordinary skill in the art to protect a hydroxyl group (e.g., at the 21- and/or 24-position) prior to a Birch reduction.

Furthermore, even assuming that a *prima facie* obviousness rejection has been set forth in the Office Action, the inventive methods as defined by the pending claims have unexpected properties that rebut the *prima facie* obviousness rejection. Claims 1-24 are directed to a method for producing a mixture of 5 $\alpha$ -pregnane derivatives (i.e., either compounds of formulae (II) and (III) (claims 1-6 and 13-18) or formulae (VI) and (VII) (claims 7-12 and 19-24)), in which, *inter alia*, the metal is present in an amount of 1.6 to 5 molar equivalents relative to the compound represented by the formula (I). Applicants unexpectedly discovered that when the amount of the reducing agent is decreased from the conventional amount, *such as the amount taught by Nakazawa et al.* (paragraph 0050), to the claimed range of 1.6 to 5 molar equivalents, a side reaction can be suppressed, and the total yield of the mixture can be increased (e.g., from 65% to 89%). Moreover, Applicants surprisingly found that the Birch reduction can be controlled when the 21-hydroxyl group is protected. See, e.g., Example 1 of the specification.

Controlling the amount of metal to the specifically claimed range and protecting the 21-hydroxyl group are not features appreciated by either Nakazawa et al. or Moriarty et al. Nakazawa et al. discloses the amount of metal as at least 2 molar equivalents or 2 to 20 molar equivalents relative to the compound to be reduced (paragraph 0050). These ranges in Nakazawa et al. represent conventional amounts of metal in a Birch reduction and are not equivalent to the claimed range of 1.6 to 5 molar equivalents. Because neither reference, in particular Nakazawa et al., recognizes any benefit to controlling the amount of metal to 1.6 to 5 molar equivalents, one cannot properly say that the claimed methods which are characterized by such features are obvious in view of the cited references, either alone or in combination.

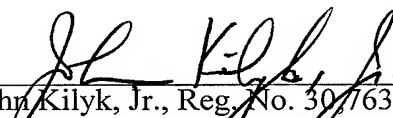


Based on the foregoing, it is evident that Nakazawa et al. does not inherently disclose the products of the claimed methods, Moriarty et al. does not provide a credible reason for protecting the 21-hydroxyl group, and the methods defined by the amended pending claims exhibit unexpected results. Each of these reasons and certainly the reasons in combination serve to rebut any *prima facie* obviousness rejection based on Nakazawa et al. and Moriarty et al. Accordingly, Applicants respectfully request that the obviousness rejection over Nakazawa et al. in view of Moriarty et al. be withdrawn.

### *Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

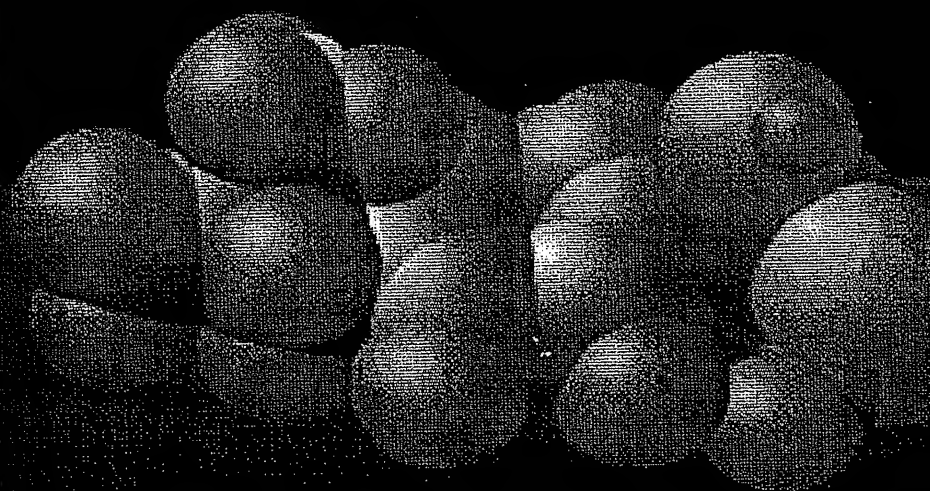


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John Kilyk, Jr., Reg. No. 30,763  
LENDIG, VOIT & MAYER, LTD.  
Two Prudential Plaza, Suite 4900  
180 North Stetson Avenue  
Chicago, Illinois 60601-6731  
(312) 616-5600 (telephone)  
(312) 616-5700 (facsimile)

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Synthetic Approaches in  
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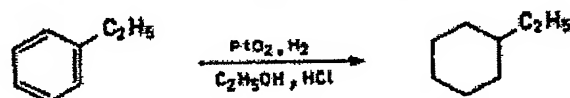
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metal hydrides reducing agents is that they are effective only for aromatic ketones, the aliphatic ketones are reduced with much lower optical purity.

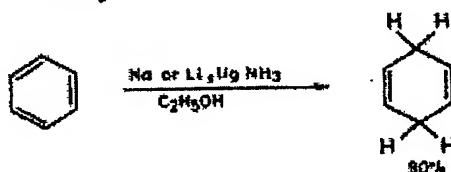
### 2.2.3 The Birch Reduction

Aromatic rings can be completely reduced by catalytic hydrogenation.

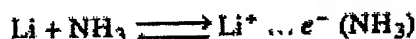


Milder conditions are successful for hydrogenation with phase transfer catalysts.

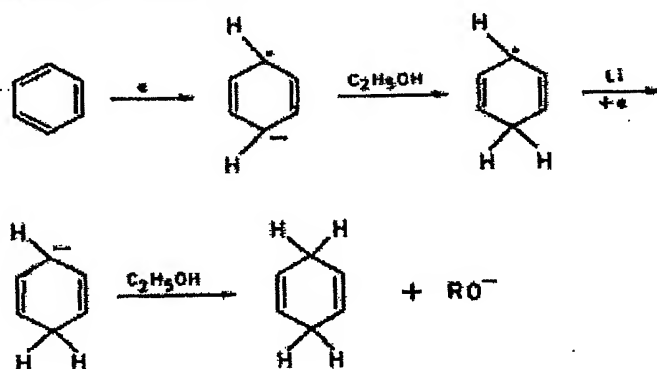
But when aromatic rings are reduced by sodium or lithium in liquid ammonia (such reductions are known as dissolving metal reductions) and in the presence of ethanol or methanol (as proton donors) the aromatic ring is only partially reduced. This reaction is one of the most fundamental reactions in organic chemistry and is called the Birch reduction.<sup>1,2</sup> The reaction is usually conducted at the boiling point of ammonia ( $-33^{\circ}\text{C}$ ). A familiar example involves the conversion of benzene to 1,4-dihydrobenzene in the presence of Na or Li/NH<sub>3</sub>.



This reaction is initiated by electron transfer:

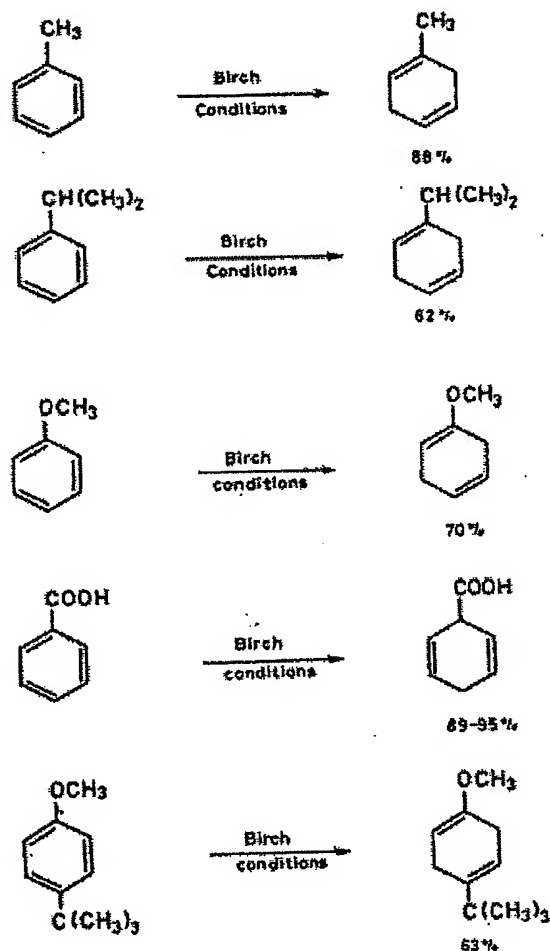


and an anion-radical is formed as an intermediate. The mechanism can be depicted in the following steps:



1. A.J. Birch, J. Chem. Soc., 430 (1944); for a review see, A.J. Birch, Quat. Rev., 4, 69 (1950).
2. For use in natural product synthesis, see J.M. Hooker and L.N. Mander, Natural Prod. Rep., 3, 35 (1986).

The mechanism of reduction involves, radical anion formation followed by protonation by an alcohol, addition of an electron and finally protonation of the cyclohexadienyl carbanion. The function of the donor is to protonate the intermediate anion-radical and thus to cut down on undesirable side-reactions such as dimerization of the radical anion and polymerization. The rate-limiting step is the protonation of the radical anion.<sup>1</sup> Birch reduction is used for the reduction of a wide variety of aromatic compounds varying in their degree of substitution and in the nature of substitution. The relative rates and regiochemistry are affected by the type of groups present on the ring. The substituents tend to stabilize or destabilize the radical anion<sup>2</sup>. Thus



1. A.P. Krapcho and A.A. Bothner-By, J. Am. Chem. Soc., 81, 3658 (1959).
2. P.W. Rabideau, Tetrahedron, 45, 1579 (1989).

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JOINT COMMISSION ON BIOCHEMICAL NOMENCLATURE\*

**NOMENCLATURE OF STEROIDS**

(Recommendations 1989)

*Prepared for publication by*

G. P. MOSS

Queen Mary College, Mile End Road, London E1 4NS, UK

\*Membership of the Commission (JCBN) during 1987-89 is as follows:

*Chairman:* J. F. G. Vliegthart (Netherlands); *Secretary:* A. Cornish-Bowden (UK);  
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P. Venetianer (Hungary); *Associate Members:* G. P. Moss (UK); J. C. Rigg (Netherlands).

Additional contributors to the formulation of these recommendations:

*Nomenclature Committee of IUB(NC-IUB)* (those additional to JCBN): H. Bielka (GDR);  
C. R. Cantor (USA); H. B. F. Dixon (UK); P. Karlson (FRG); K. L. Loening (USA); W.  
Saenger (FRG); N. Sharon (Israel); E. J. van Lenten (USA); S. F. Velick (USA); E. C.  
Webb (Australia).

*Membership of Expert Panel:* P. Karlson (FRG, *Convener*); J. R. Bull (RSA); K. Engel  
(FRG); J. Fried (USA); H. W. Kircher (USA); K. L. Loening (USA); G. P. Moss (UK);  
G. Popják (USA); M. R. Uskokovic (USA).

Correspondence on these recommendations should be addressed to Dr. G. P. Moss at the  
above address or to any member of the Commission.

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# Nomenclature of steroids (Recommendations 1989)

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The recommendations of steroid nomenclature have a long history, a brief account of which was given in definitive rules for the nomenclature of steroids (1971) [1]. Since that time, many of the principles developed for the nomenclature of steroids have been generally adopted and have become part of the IUPAC nomenclature of organic compounds, especially section F [3]. The aim of the present document, prepared with the help of a panel of experts, is a revision of the recommendations in the light of new developments and current practice.

The main changes are as follows: (i) modifications, where appropriate, to conform to section F (Natural Products) of the IUPAC nomenclature [3]; (ii) a wider use of the *R,S* system for designating the stereochemistry in the side chain; (iii) the incorporation of the new recommendations (1981) for the nomenclature of vitamin D [5]; and (iv) the omission of most steroid alkaloid and steroid-like triterpenoids as it is intended that they should be treated in an appendix to IUPAC nomenclature, section F [3]. Significant changes are indicated by ▲ in the margin for major additions and Δ for minor revisions.

These recommendations are numbered 3S-1, 3S-2, 3S-3, etc., the initial 3 denoting that this is the third revised set of recommendations.

### 3S-1. GENERAL

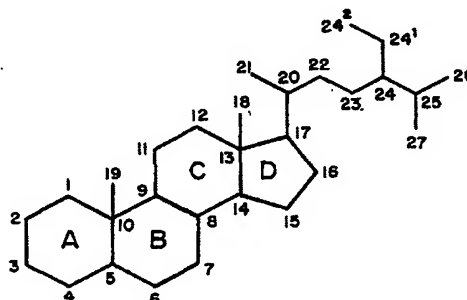
#### ▲ 3S-1.0. Definition of steroids and sterols

Steroids are compounds possessing the skeleton of cyclopenta[*a*]phenanthrene or a skeleton derived therefrom by one or more bond scissions or ring expansions or contractions. Methyl groups are normally present at C-10 and C-13. An alkyl side chain may also be present at C-17. Sterols are steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane. Additional carbon atoms may be present in the side chain.

▲ *Note* This definition of sterols is rather restrictive. However, a less restrictive definition would cause difficulties, e.g. androst-16-en-3 $\beta$ -ol is normally not called a sterol and should not fall under the definition.

#### 3S-1.1. Numbering and ring letters

Steroids are numbered and rings are lettered as in formula 1. If one of the two methyl groups attached to C-25 is substituted it is assigned the lower number (26); if both are substituted, that carrying the substituent cited first in the alphabetical order is assigned the lower number. For trimethyl steroids see Recommendation 3S-2.4, Note 2.



(1)

▲ *Note* The numbers 28, 29 and 30 are now assigned to the additional methyl groups at C-4 and C-14 in triterpenoids, e.g. lanosterol (see 3S-2.4, note 2). Therefore, the carbon atoms at the methyl or ethyl groups at C-24 had to be renumbered. The system adopted here allows also numbering of other carbon atoms attached to the steroid skeleton. If two side chains are attached to the same carbon atom, the shorter one receives primed numbers, e.g. 17<sup>1</sup> (see 3S-2.7 and 3S-2.8).

#### 3S-1.2. Absent carbon atoms

If one or more of the carbon atoms shown in 1 is not present and a steroid name is used, the numbering of the remainder is undisturbed.

#### 3S-1.3. Absolute configuration

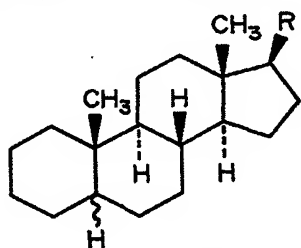
The absolute stereochemistry of a steroid is defined by the parent name for some chiral centres (see 3S-1.5) and by  $\alpha$ ,  $\beta$ , *R* or *S* for other centres (see 3S-1.4 and 3S-1.6). When the configuration at one or more centres is not known, this is indicated by the Greek letter(s)  $\xi$  ( $\chi$ ) prefixed by the appropriate locant(s).

#### 3S-1.4. Orientation of projection formulae

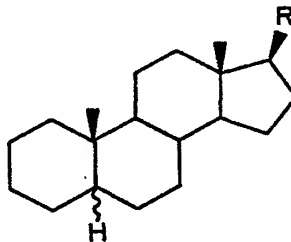
When the rings of a steroid are denoted as projections onto the plane of the paper, the formula is normally to be oriented as in 2a. An atom or group attached to a ring depicted as in the orientation 2a is termed  $\alpha$  (alpha) if it lies



below the plane of the paper or  $\beta$  (beta) if it lies above the plane of the paper. In formulae, bonds to atoms or groups lying below the plane of the paper ( $\alpha$ ) are shown as broken lines (----- or - - - - -), and bonds to atoms or groups lying above the plane of the paper ( $\beta$ ) are shown as solid lines (preferably thickened, — or ———). Bonds to atoms or groups whose configuration is not known are denoted by wavy lines (~~~~~).



(2a)

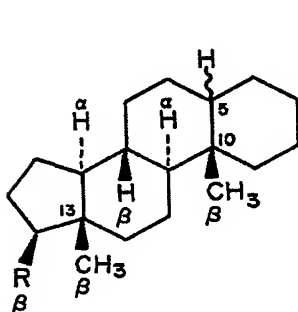


(2b)

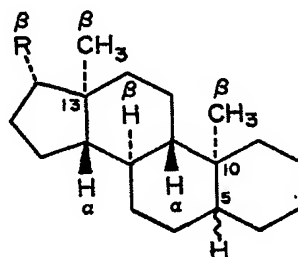
#### Notes

- ▲ 1) In the formula 2a given above, all angular methyl groups and H atoms have been written out explicitly. However, when there is no ambiguity, methyl groups may also be indicated by a bond without lettering as in 2b, a practice followed in other fields. Likewise, the hydrogen atoms at the bridgehead C-8, C-9 and C-14 may be omitted if there is no ambiguity, i.e. if they are oriented  $\delta\beta, 9\alpha, 14\alpha$ . If one of the hydrogen atoms is replaced, e.g. by a fluorine atom, care must be taken in the correct use of broken ( $\alpha$ ) and bold ( $\beta$ ) lines. The bond to a bridgehead hydrogen atom should never be drawn without the H.

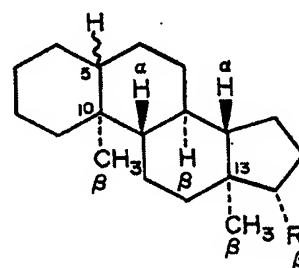
- 2) Projections of steroid formulae should not be oriented as in formulae 2c, 2d or 2e unless circumstances make it obligatory, e.g. in dimers formed photochemically [4].



(2c)



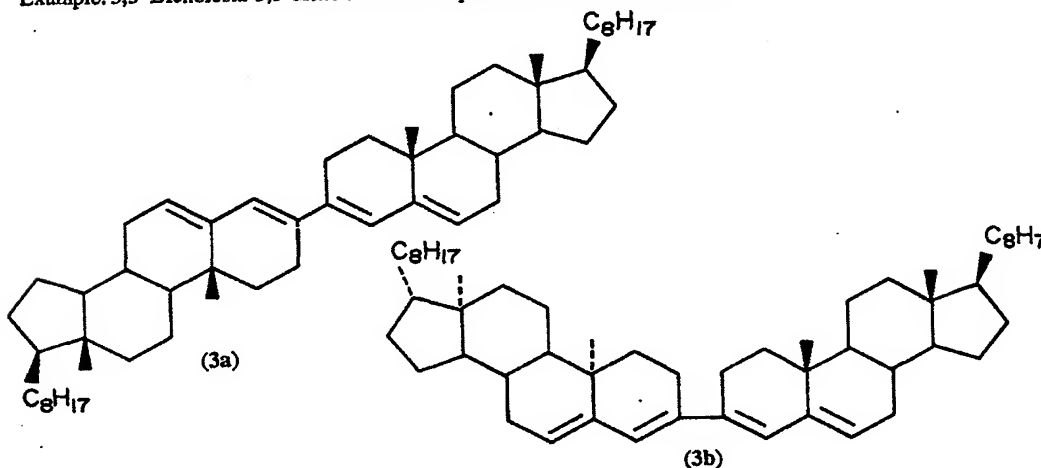
(2d)



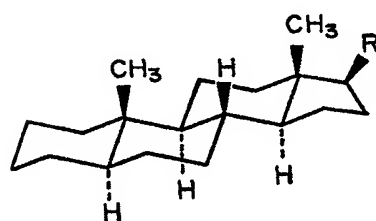
(2e)

- 3) With the preferred orientation 2a, and with 2c, which is only rotated in the plane of the paper,  $\alpha$ -bonds appear as broken lines and  $\beta$ -bonds as solid (thickened) lines. The reverse is true for 2d and 2e; therefore, orientation 2c is preferred over 2d or 2e if there is a choice. Wavy lines denote  $\xi$ -bonds for all orientations of the formula.

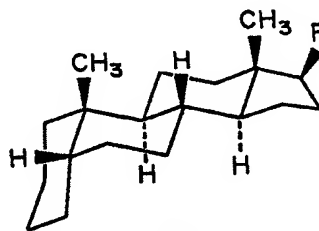
Example: 3,3'-Bicholesta-3,5-diene should be represented as 3a but not as 3b.



4) A perspective representation of the stereochemistry of formula 2 as in 2f or 2g may also be used:



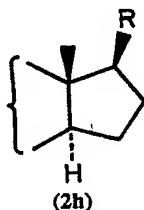
(2f)  
A 5 $\alpha$ -steroid



(2g)  
A 5 $\beta$ -steroid

When steroid formulae are drawn in this way, bonds pointing upwards are, by convention, drawn bold and bonds pointing downwards are drawn broken; these representations correspond to the  $\beta$ - and  $\alpha$ - bonds of projection formulae such as 2a and do not conform to the general practice that bold and broken lines denote bonds projecting respectively above and below the plane of the paper. Note, however, that the general practice is followed with chair and boat forms of spirostans (see Recommendation 3S-3.3).

△ 5) To save space and to emphasise the relevant portion of the steroid formula a brace may be used. For example 2h only shows ring D and the side chain at C-17 but in this context the portion to the left of the brace may be assumed to be the rest of an androstane ring system as in formulae 2a-g. In other contexts, for example, it might represent the rest of an estrane ring system, including any substituents, and double bonds present in that portion.



### 3S-1.5. Stereochemistry of ring junctions and side-chain attachment

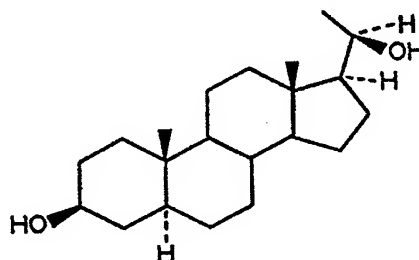
Unless implied or stated to the contrary (see Recommendations 3S-3, 3S-4.1 and 3S-5), use of a steroid name implies that atoms or groups attached at the bridgehead positions 8, 9, 10, 13 and 14 are oriented as shown in formula 2a (i.e. 8 $\beta$ , 9 $\alpha$ , 10 $\beta$ , 13 $\beta$ , 14 $\alpha$ ), and a side chain attached at position 17 is assumed to be  $\beta$ -oriented (see notes below). The configuration of hydrogen (or a substituent) at the bridgehead position 5 is always to be designated by adding  $\alpha$ ,  $\beta$  or  $\xi$  after the numeral 5, this numeral and letter being placed immediately before the stem name. The stereochemistry of substituents attached to the tetracyclic system A-D is stated by adding  $\alpha$ ,  $\beta$  or  $\xi$  after the respective numerals denoting their position.

#### Notes

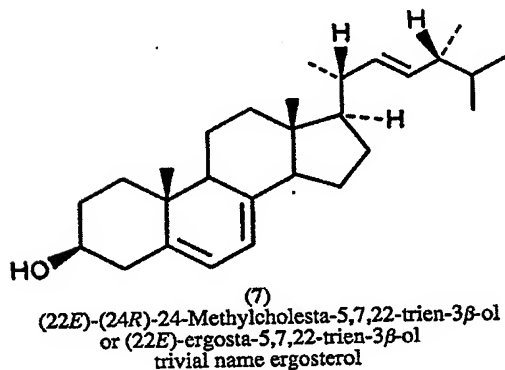
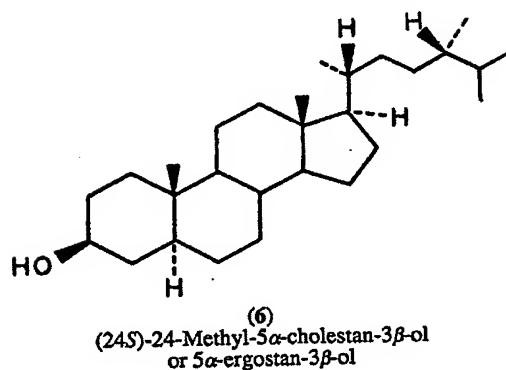
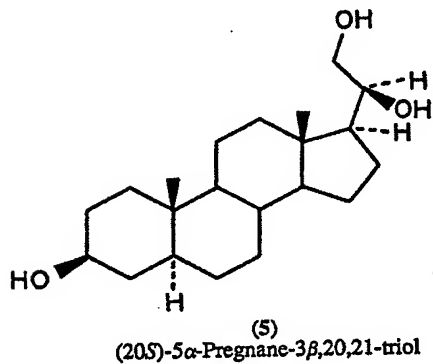
- 1) If one of the bridgehead hydrogen atoms is replaced it may be desirable (although not necessary) to restate the stereochemistry, e.g. 9 $\alpha$ -fluoro-5 $\alpha$ -pregnane instead of 9-fluoro-5 $\alpha$ -pregnane.
- 2) For the purpose of this Recommendation, a carboxyl group at position 17 is treated as a substituent (see Recommendation 3S-4.1).
- 3) If two carbon chains are attached at position 17, see Recommendations 3S-2.7 and 3S-2.8.

### ▲ 3S-1.6. Stereochemistry of substituents in the side chain

The stereochemistry of substituents on the steroid side chain is described by the sequence rule procedure (see [3], section E), unless implied by the name (see 3S-2.4 and Table 1). Examples:



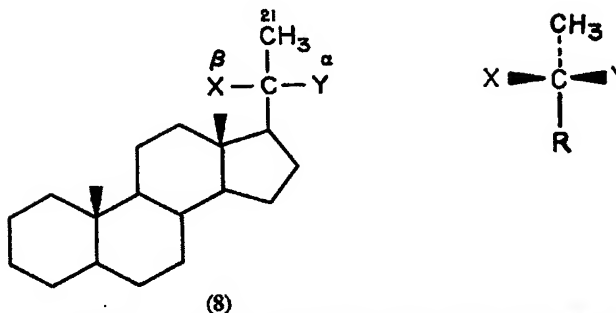
(4)  
(20R)-5 $\alpha$ -Pregnane-3 $\beta$ ,20-diol



#### Notes

1) The backbone of a side chain at C-17 is best denoted as in the plane of the paper (lines of ordinary thickness), the 17-20 bond being similarly denoted. Stereochemistry due to substituents on the chain is then indicated by the customary thick or broken lines denoting bonds that project, respectively, above and below the plane of the paper. In formulae the representation of the side chain is drawn as in examples 6 and 7 in preference to those used in the previous edition of this document [1].

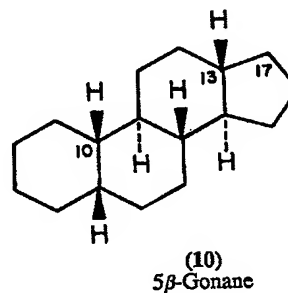
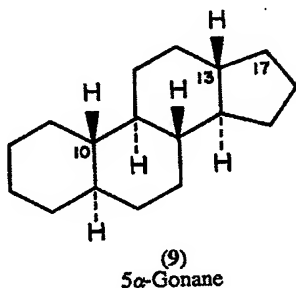
2) In the pregnane series, the stereochemistry at C-20 was formerly designated as 20α or 20β. This convention was based on a Fischer projection with the highest number at the top, as given in formula 8. This nomenclature is now discouraged for specific compounds in favour of the *R,S* system, which can be generally used for all chiral centres in the side chain(s). However, as α and β are independent of substituents at neighbouring atoms they are retained for the corresponding enzyme names, e.g. 20α-hydroxysteroid dehydrogenase.



### 3S-2. FUNDAMENTAL CARBOCYCLES, UNSATURATION AND ALKYL SUBSTITUTION AT C-17

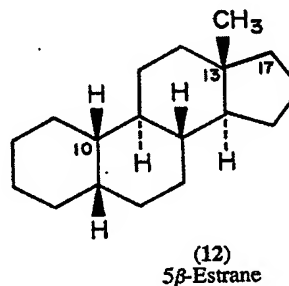
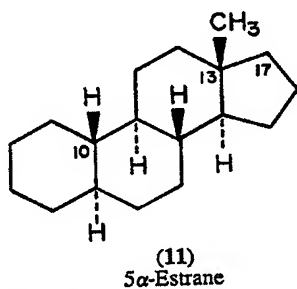
#### 3S-2.1. *Gonane*

The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and without a side chain at C-17 is named gonane; see formulae 9 and 10.



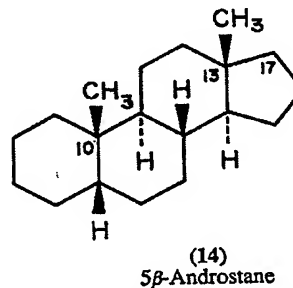
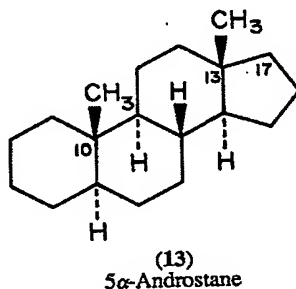
#### 3S-2.2. *Estrane* (oestrane)

The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and without a side chain at C-17 is named estrane (alternative spelling: oestrane), as shown in 11 and 12.



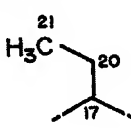
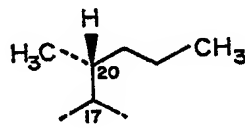
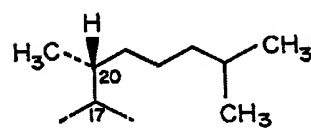
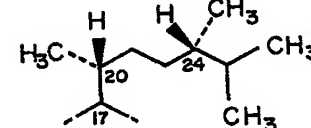
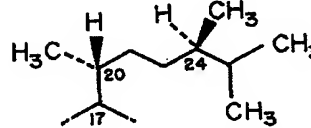
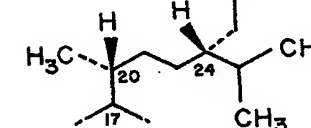
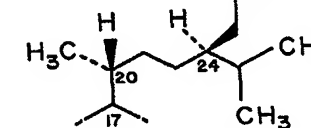
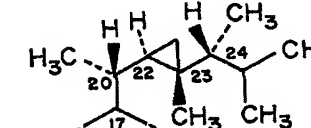
#### 3S-2.3. *Androstane*

The hydrocarbon with methyl groups at C-10 and C-13 but without a side chain at C-17 is named androstane 13 and 14.



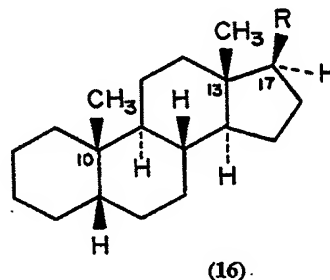
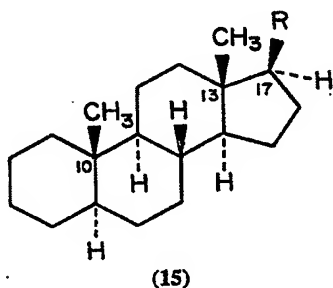
**Note** For the names of hydrocarbons having a methyl group attached to C-10 and a hydrogen atom attached to C-13, or compounds where an ethyl group replaces a methyl group, see 3S-6. Ring expansion or contraction is covered by 3S-7.

Table 1. *Hydrocarbons with side chain at C-17*

Side chain	Configuration	5 $\alpha$ -Series (15)	5 $\beta$ -Series (16)
	-	5 $\alpha$ -pregnane (not allopregnane)	5 $\beta$ -pregnane
	20R	5 $\alpha$ -cholane (not allocholane)	5 $\beta$ -cholane
	20R	5 $\alpha$ -cholestane (not coprostanane)	5 $\beta$ -cholestane
	20R,24S	5 $\alpha$ -ergostane	5 $\beta$ -ergostane
	20R,24R	5 $\alpha$ -campestanane	5 $\beta$ -campestanane
	20R,24S	5 $\alpha$ -poriferastane	5 $\beta$ -poriferastane
	20R,24R	5 $\alpha$ -stigmastane	5 $\beta$ -stigmastane
	20S,22R,23R,24R	5 $\alpha$ -gorgostane	5 $\beta$ -gorgostane

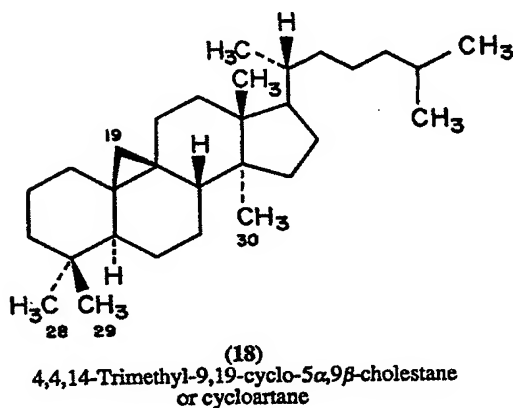
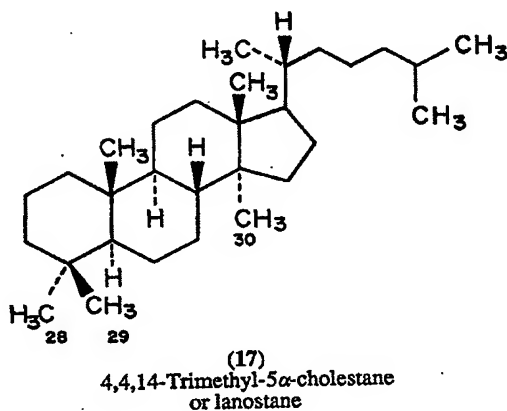
## 3S-2.4. Parent hydrocarbons with side chain at C-17

The names used for the hydrocarbons 15 and 16 with methyl groups at both C-10 and C-13 and a side chain R are listed in Table 1.



## Notes

- 1) The names of the hydrocarbons given in Table 1 imply the configuration at the chiral centres in the side chain as given in the second column. The conventions of the sequence rule, however, mean that *R* may change to *S* without a change at the relevant atom when there is a change in the substitution or unsaturation, e.g. compare 6 and 7.
- 2) Some tetracyclic triterpenoids may be regarded as trimethyl steroids, the three additional methyl groups being numbered 28 (attached to C-4 with  $\alpha$ -configuration), 29 (attached to C-4 with  $\beta$ -configuration) and 30 (attached to C-14); this numbering corresponds to that used for the triterpenoids. This type of nomenclature is especially useful for the parent hydrocarbons of biogenetic precursors of steroids. For example, lanostane 17 is 4,4,14-trimethyl-5 $\alpha$ -cholestane, the former name implying the 5 $\alpha$ ,8 $\beta$ ,9 $\alpha$ ,10 $\beta$ ,13 $\beta$ ,14 $\alpha$ ,17 $\beta$ ,20 $R$  configuration. The change of configuration at C-9 in cycloartane 18 is implied in the name, although it must be specified if called 4,4,14-trimethyl-9,19-cyclo-5 $\alpha$ ,9 $\beta$ -cholestane.

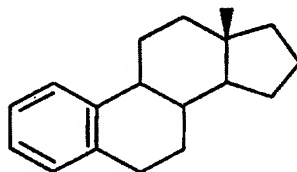


3) For the names of hydrocarbons that are related to those given in Table 1 by the addition or removal of one or more carbon atoms, see 3S-6. For ring expansion or contraction see 3S-7.

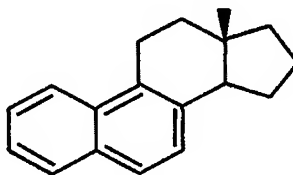
### 3S-2.5. Unsaturation

Unsaturation is indicated by changing -ane to -ene, -adiene, -yne etc., or -an- to -en-, -adien-, -yn- etc. Examples:

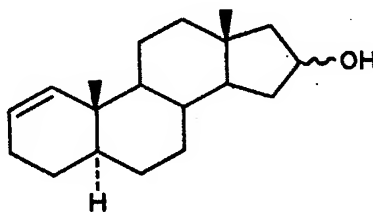
Androst-5-ene, not 5-androstene  
 $5\alpha$ -Cholest-6-ene  
 $5\beta$ -Cholesta-7,9(11)-diene  
 $5\alpha$ -Cholest-6-en- $3\beta$ -ol



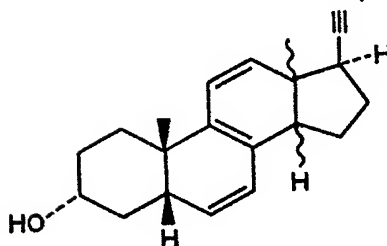
(19)  
Estra-1,3,5(10)-triene



(20)  
Estra-1,3,5,7,9-pentaene



(21)  
 $5\alpha$ -Androst-1-en- $16\beta$ -ol



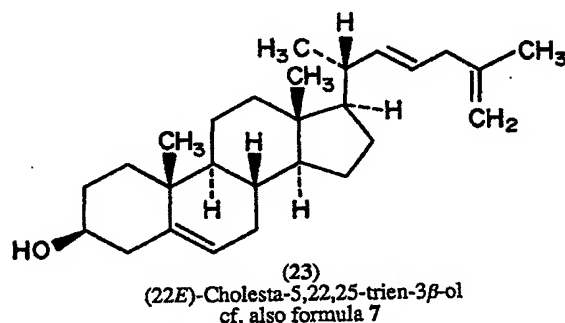
(22)  
 $5\beta,13\xi,14\xi$ -Pregna-6,8,11-trien-20-yn- $3\alpha$ -ol

### Notes

- ▲ 1) It is now recommended that the locant of a double bond is always adjacent to the syllable designating the unsaturation.
- 2) If there is a choice of locants, single ones are preferred to compound locants, e.g. *estra-5,7,9-triene* is preferred to *estra-5(10),6,8-triene*.
- 3) The use of  $\Delta$  (Greek capital delta) is not recommended to designate unsaturation in individual names. It may be used, however, in generic terms, like ' $\Delta^5$ -steroids'.
- △ 4) When an unsubstituted 25(26)-double bond is present the two methyl groups attached at position 25 are numbered 26 and 27 with the lower number for the methyl group *trans* to position 23.

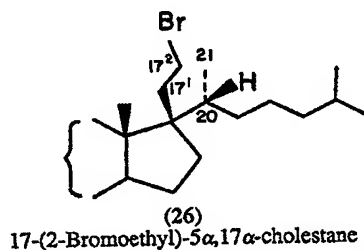
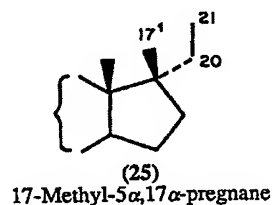
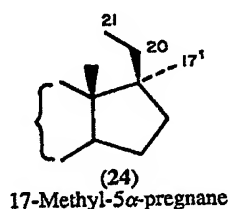
## 3S-2.6. Stereochemistry of double bonds

The stereochemistry of double bonds in the side chain should be indicated using the *E,Z* convention (cf. Recommendation E-2.2 in [3]). The same applies to the seco compounds of the vitamin D series (see 3S-9).  
Example:



## 3S-2.7. Steroids with a side chain as part of the parent carbocycle and an alkyl substituent at C-17

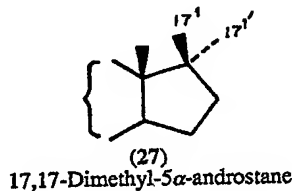
If a steroid has two carbon chains attached at position 17 and one of them is included in Table 1, the compound is named as a 17-alkyl derivative of that steroid. If both side chains at C-17 are in Table 1, then the larger one is used, or the one in the normal configuration, e.g. 17-ethyl-5α-cholestane, 17-ethyl-5α-pregnane (not 17-ethyl-Δ-5α,17α-pregnane). The carbon atoms of the alkyl substituent may be numbered by a superscript number added to the number of the atom to which it is attached, e.g. 17<sup>1</sup>, 17<sup>2</sup>... etc. (cf. example 26). Examples:



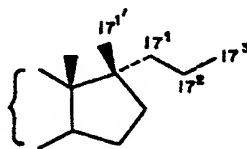
△ *Note* Locants with superscript numbers are intended for the identification of the atoms e.g. in <sup>13</sup>C-nmr spectral assignments, not as locants for further substitution e.g. oxymetholone [an international non-proprietary name (INN) see 3S-4.10 and Appendix] is 17β-hydroxy-2-(hydroxymethylene)-17α-methyl-5α-androstan-3-one, not 2<sup>1</sup>,17β-dihydroxy-17α-methyl-2-methylene-5α-androstan-3-one.

## 3S-2.8. Steroids with two alkyl substituents at C-17

If a steroid has two carbon chains attached at position 17, neither of which is included in Table 1, the compound is named as a 17,17-disubstituted androstane. Examples:







(28)

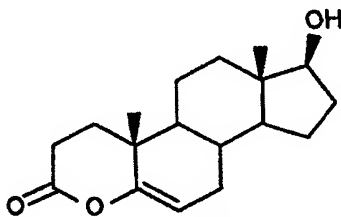
17β-Methyl-17α-propyl-5α-androstane

*Notes*

- 1) Some steroids of this class can be related to a fundamental structure listed in Table 1 by applying the rules of chain lengthening and shortening (3S-6). Thus structure 28 could be called 17-methyl-21,24-dinor-5α,17α-choleane. This procedure is not recommended as it often yields cumbersome names.
- △ 2) The carbon atoms of the alkyl substituents may be numbered by a superscript number added to the number of the steroid skeletal atom to which it is attached. The shorter of the two substituent chains receives primed superscript numbers. If the two substituent chains are of equal length and attached to the steroid ring system the substituent on the β-face has primed superscript numbers. If the two substituent chains are attached to the side chain of the steroid and are of equal length but one is further substituted the other chain has primed superscript numbers. In the absence of further substitution the *pro-S* group has primed superscript numbers.
- △ 3) Locants with superscript numbers are intended for the identification of the atoms e.g. in <sup>13</sup>C-nmr spectral assignments, not as locants for further substitution (see note to 3S-2.7).

3S-2.9. *Replacement of carbon atoms by hetero atoms*

When in the carbon skeleton of a steroid a carbon atom is replaced by a hetero atom, the replacement (oxa-aza) system of nomenclature is used with steroid names and numbering (cf. Recommendation B-4 in [3]). Example:

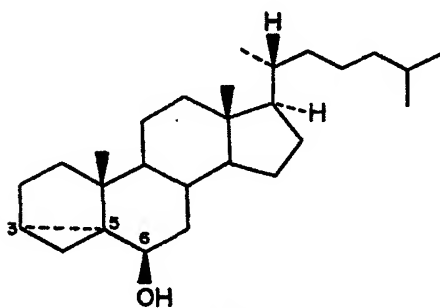


(29)

17β-Hydroxy-4-oxaandrost-5-en-3-one

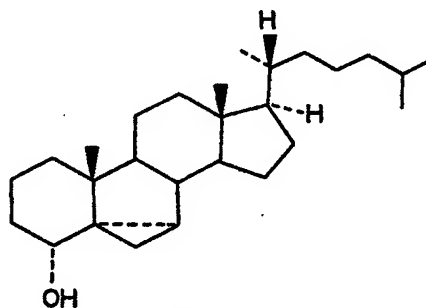
3S-2.10 *Additional rings formed within the steroid skeleton*

When an additional ring is formed by means of a direct link between any two carbon atoms of the steroid ring system or the attached side chain, the name of the steroid is prefixed by *cyclo*; this prefix is preceded by the numbers of the positions joined by the new bond and Greek letter (α, β, or δ) denoting the configuration associated with the new bond, unless that designation is already implicit in the name. Examples:



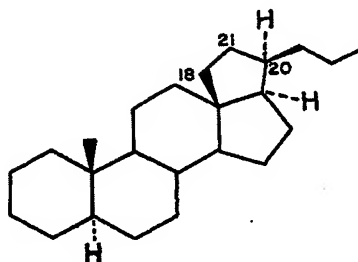
(30)

3α,5-Cyclo-5α-cholestan-6β-ol



(31)

5,7α-Cyclo-5α-cholestan-4α-ol



(32)  
(20R)-18,21-Cyclo-5α-choleane

*Note* Compound 30 is also known as i-cholesterol; likewise the 3,5-cyclosteroids are often called i-steroids.

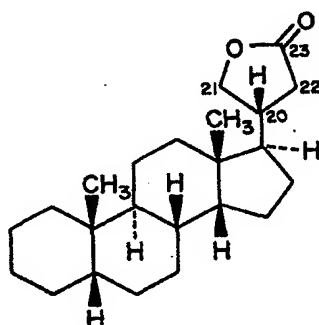
### 3S-3. STEROIDS WITH HETEROCYCLIC RINGS IN THE SIDE CHAIN

#### 3S-3.0. General definitions

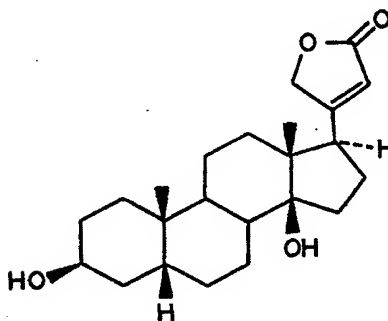
Many important naturally occurring steroids contain one or more additional heterocyclic ring(s), fused or attached to ring D, formed by modifications of the side chain. These steroids can be grouped into the following families: (a) cardanolides, (b) bufanolides, (c) spirostans, (d) furostans, (e) steroid alkaloids.

#### 3S-3.1. Cardanolides

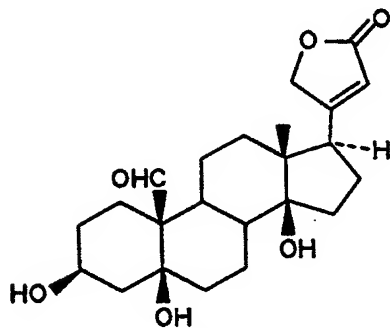
The name cardanolide is used for the compound of structure 33, i.e. the parent compound of digitaloid lactones with the configuration illustrated. The 14β-configuration as well as the 20R-configuration are implied in the name.  
Examples:



(33)  
5β-Cardanolide



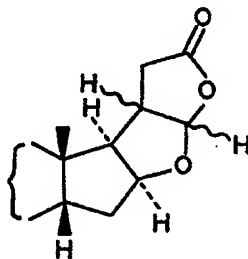
(34)  
3β,14-Dihydroxy-5β-card-20(22)-enolide  
trivial name: digitoxigenin



(35)  
3β,5,14-Trihydroxy-19-oxo-5β-card-20(22)-enolide  
trivial name: strophanthidin

Names such as card-20(22)-enolide are used for the naturally occurring unsaturated lactones of this type. The names 14,21- and 16,21-epoxycardanolide are used for the compounds containing a 14,21- or a 16,21-oxygen bridge respectively, as shown in 36.

- ▲ **Note** The former recommendation that the configuration at C-14 must always be stated as an affix is abandoned; 14β is implied unless otherwise stated. See also note 1 to 3S-1.5.

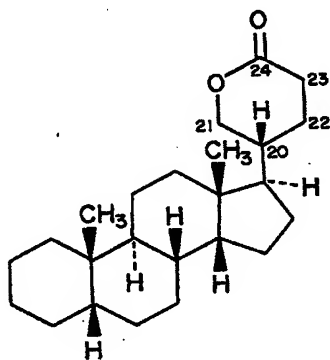


(36)  
A 16β,21ξ-epoxy-20ξ-cardanolide

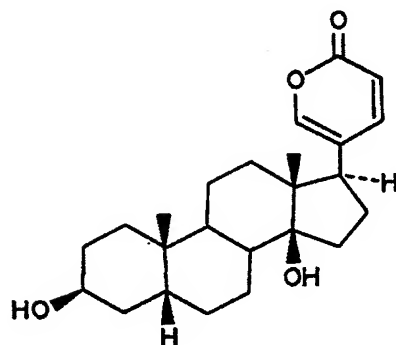
### 3S-3.2. Bufanolides

The name bufanolide is used for the compound of structure 37, the parent compound of the squill-toad poison group of lactones, with the configurations 14β,20R as shown implied in the name. Unsaturated derivatives are named by replacing the suffix -anolide by -enolide, -adienolide, etc.; thus the name bufa-20,22-dienolide is used for the naturally occurring doubly unsaturated lactones.

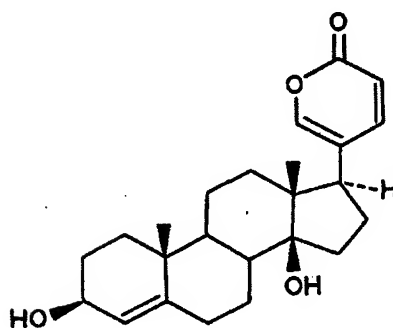
- ▲ **Note** As with cardanolides, the recommendation to always state the configuration at C-14 is abandoned. See also note (1) to 3S-1.5. Examples:



(37)  
5β-Bufanolide



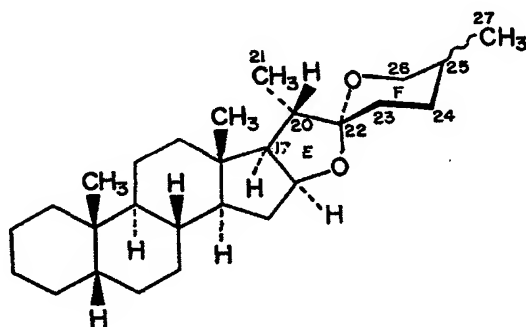
(38)  
3β,14-Dihydroxy-5β-bufa-20,22-dienolide  
trivial name: bufalin



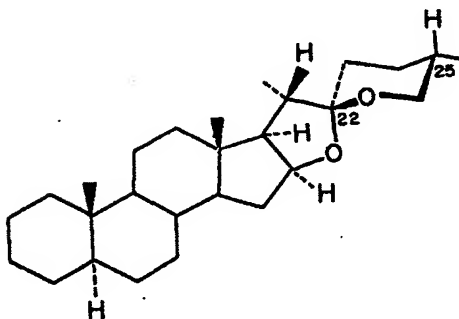
(39)  
3β,14-Dihydroxybufa-4,20,22-trienolide  
trivial name: scillarenin

### 3S-3.3. Spirostans

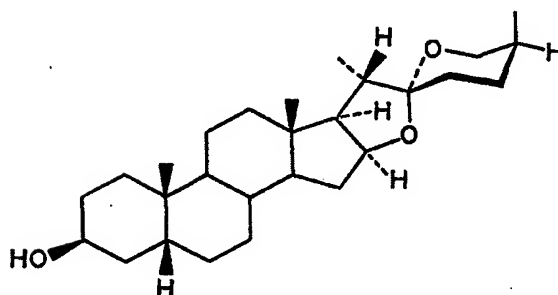
The name spirostan is used for compounds of structure 40 (this is a 16,22:22,26-diepoxycholestane); this name specifies the configuration shown for all the asymmetric centres except positions 5 and 25. A prefix 5α- or 5β- is added in the usual way (see Recommendation 3S-1.5). Configurations at C-16 and C-17, if different from those shown in formula 40, are designated by 16β(H) and 17β(H). Configurations at C-20 and C-22, if different from those shown in formula 40, are designated by the sequence-rule procedure (see Section E in [3]) or, if unknown, by ξ. Steric relations of substituents at C-23, C-24 or C-26 are in all cases designated by the sequence-rule procedure or, if unknown, by ξ. Examples:



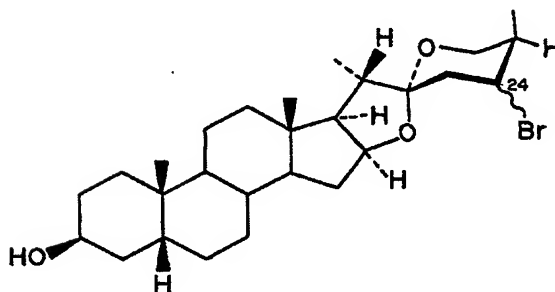
(40)  
5β-Spirostan



(41)  
(22*S*,25*S*)-5 $\alpha$ -Spirostan



(42)  
(25*S*)-5 $\beta$ -Spirostan-3 $\beta$ -ol  
trivial name: sarsasapogenin



(43)  
(25*R*)-24 $\beta$ -Bromo-5 $\beta$ -spirostan-3 $\beta$ -ol

#### Notes

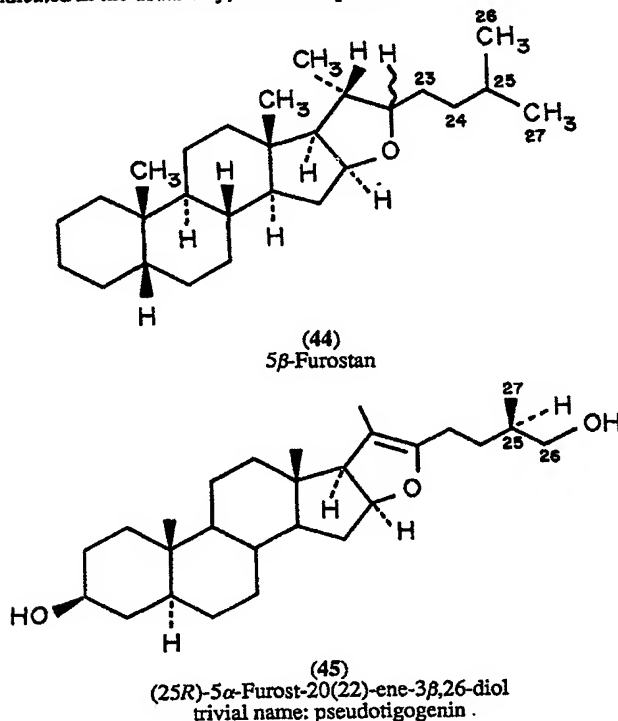
1) Although ring E, like rings A, B, C and D, can conveniently be shown by projection on to the plane of the paper, ring F cannot be adequately represented in this way since C-23, C-24 and C-26 and the oxygen atom lie in a plane that is perpendicular to the plane of the paper. Ring F is conveniently drawn as in formulae 40-43; in formula 40, for instance, the broken line from C-22 to oxygen denotes that the oxygen atom and C-26 of ring F lie behind the plane of the paper and that consequently C-23 and C-24 lie in front of the plane of the paper (configuration *R* at C-22). In formula 41 the configuration at C-22 is reversed and must be stated in the name as 22*S*. It is conventional to draw ring F as a chair, but this conformation is not implied in the name spirostan. Whatever the conformation of ring F, C-27 and the 25-hydrogen atom may be considered to lie in the plane of the paper and so cannot be denoted by broken or thickened lines. In 42 the methyl group is axial (above the general plane of ring F), and in 41 it is equatorial (in the general plane of ring F).

2) The *R,S* specification may also be affected by substituents attached to ring F or C-27, as in compound 43 (cf. 42).

3S-3.4. *Furostans*

The name furostan is used for the compound of structure 44 (16,22-epoxycholestane); this name specifies the configurations at all the asymmetric centres except position 5, 22 and (if position 26 is substituted) also 25. Configuration at C-5 is designated by use of  $\alpha$  or  $\beta$  in the usual way (see Recommendation 3S-1.5), and configurations at C-22 and, if necessary, C-25 by the sequence-rule procedure, or in all these cases by  $\xi$  if unknown.

Substituents are indicated in the usual way, as in example 45.

3S-3.5. *Steroid alkaloids*

If systematic names for steroid alkaloids are desired, they should be derived from pregnane, cholestane or some other parent name given in Table 1.

Trivial names for the parent saturated structures of steroid alkaloids are so chosen that they end in -anine. In the case of unsaturated compounds, this ending is changed to -enine, -adienine, etc. as appropriate.

An extensive treatment of the nomenclature of steroid alkaloids is beyond the scope of these recommendations. A special appendix to section F of ref. 3 dealing with these problems is in preparation.

## 3S-4. FUNCTIONAL GROUPS

3S-4.0. *General*

Nearly all biologically important steroids are derivatives of the parent hydrocarbons (cf. Table 1) carrying various functional groups. Their nomenclature follows the general recommendations of the nomenclature of organic compounds (Sections C and D in [3]). However, there are some special problems in the application of these recommendations to natural products like steroids. Therefore, and for the benefit of the biochemist not so familiar with the recommendations of substitutive nomenclature, these are outlined and exemplified here. For full details, the reader is referred to the IUPAC Recommendations [3].

Most substituents can be designated either as suffixes or prefixes; some, however, the commonest being halogens, alkyl groups (see 3S-2.7 and 3S-2.8) and alkoxy groups, can only be designated as prefixes. Lists of these two types are given in Tables I and II respectively section C-10 of [3].

When possible, one type of substituent must be designated as suffix. When more than one type is present that could be designated as suffix only one type may be so expressed and the other types must be designated as prefixes. The choice for suffix is made according to an order of preference that is laid down in [3]; the most important part of this order, for steroids, is as follows in decreasing preferences: onium salt, acid, lactone, ester, aldehyde, ketone, alcohol, amine.

Suffixes are added to the name of the saturated or unsaturated parent system (see 3S-2.5), the terminal e of -ane, -ene, -yne, -adiene etc. being elided before a vowel (presence or absence of numerals has no effect on such elisions).

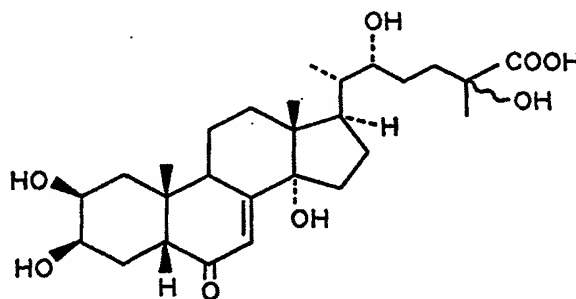
The following recommendations are on these principles. In this section, the formulae of examples correspond to 2b, i.e. the methyl groups are indicated by a bond without lettering, and the hydrogen atoms at C-8, C-9 and C-14 are omitted.

### 3S-4.1. Acids, salts and esters

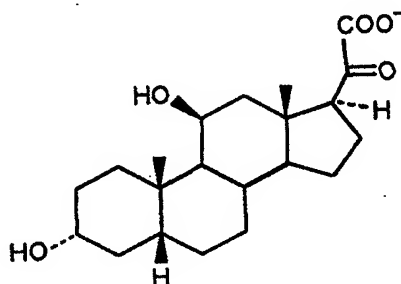
Acids, their salts and esters are generally named by use of suffixes.

a) If a methyl group is changed into a carboxyl group, the suffix is -oic acid; it is preceded by the appropriate locant. In biochemical papers, these compounds are often named as anions, the counter-ion being unspecified; in this case, the suffix is -oate. Examples:

11-Oxo-5 $\alpha$ -cholan-24-oic acid

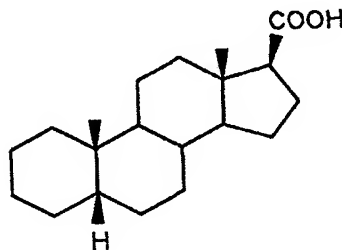


(46)  
(22*R*)-2 $\beta$ ,3 $\beta$ ,14,22,25 $\xi$ -Pentahydroxy-6-oxo-5 $\beta$ -cholest-7-en-26-oic acid  
trivial name: ecdysoneic acid

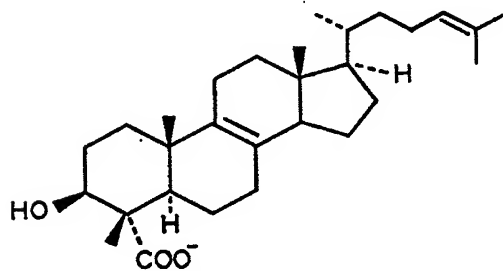


(47)  
3 $\alpha$ ,11 $\beta$ -Dihydroxy-20-oxo-5 $\beta$ -pregnan-21-oate

b) If an acid is formed by substitution of a hydrogen atom in  $\text{>CH}$ ,  $\text{>CH}_2$  or  $\text{-CH}_3$  by a carboxyl group, i.e.  $\text{>C-COOH}$ ,  $\text{>CH-COOH}$  or  $\text{-CH}_2\text{-COOH}$  the suffix is -carboxylic acid or, in the ion form, -carboxylate. Note that in this case the acid contains one more carbon atom than the parent compound. Examples:



(48)  
5 $\beta$ -Androstane-17 $\beta$ -carboxylic acid



(49)  
3β-Hydroxy-4β-methyl-5α-cholesta-8,24-diene-4α-carboxylate  
or 3β-hydroxy-30-norlanosta-8,24-dien-28-oate

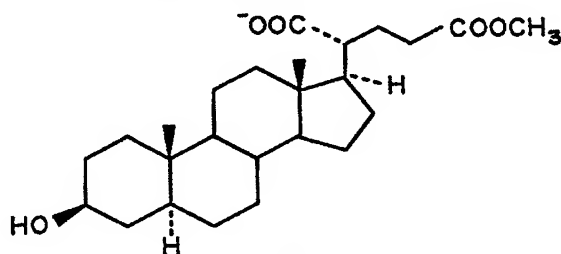
△ *Note* Compound 48 was formerly called 5β,17α(H)-etianic acid. This name, etianic acid, is now abandoned.

c) Names of salts are formed by stating the cation and using, as a separate word, the ionic form of the name of the acid. Example:

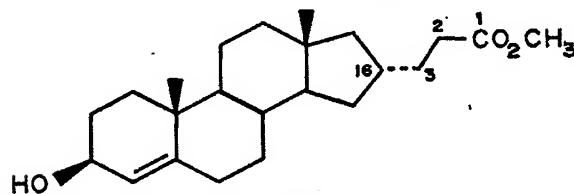
Sodium 5α-cholan-24-oate

d) Esters are conveniently named in a similar way. Examples:

Methyl 5β-androstane-17β-carboxylate  
Diethyl 5α-cholane-21,24-dioate



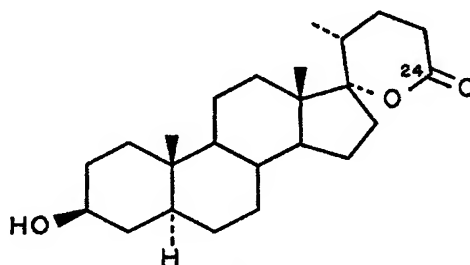
(50)  
24-Methyl 3β-hydroxy-5α-cholane-21,24-dioate



(51)  
Methyl 3-(3β-hydroxyandrost-4-en-16α-yl)propanoate

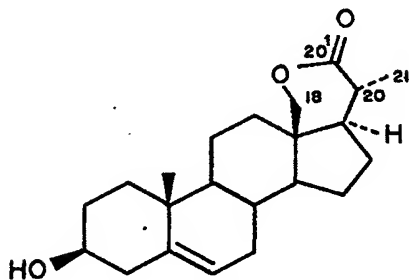
### 3S-4.2. Lactones

a) Lactones, other than cardanolides and bufanolides, are named by changing the ending -ic acid or -carboxylic acid of the name of the hydroxy acid to -lactone or -carbolactone respectively, preceded by the locant of the acid group and then the locant of the hydroxyl group. The lactonised hydroxyl group is not stated separately. Examples:

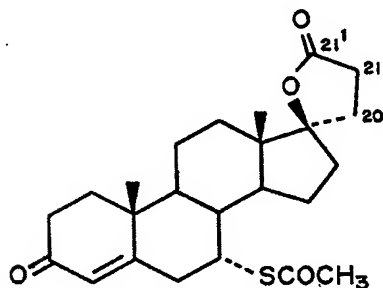


(52)  
3β-Hydroxy-5α-cholano-24,17-lactone





(53)  
(20R)-3β-Hydroxypregn-5-ene-20,18-carbolactone



(54)  
7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone  
international non-proprietary name: spironolactone

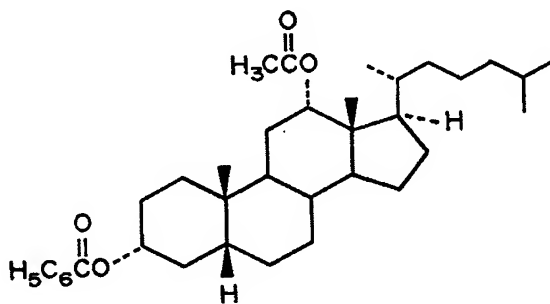
*Note* In examples 53 and 54 the suffix carbolactone corresponds to a substituent with an additional carbon atom which is numbered accordingly (see 3S-2.7). If example 53 was called 3β-hydroxy-23,24-dinorchol-5-ene-21,18-lactone (name not recommended), then the lactone carbonyl would be C-21 (see 3S-6.2 for use of nor). Similarly, if example 54 was called 7α-acetylthio-3-oxo-21a-homo-17-pregn-4-ene-21a,17-lactone (name not recommended), then the lactone carbonyl would be C-21a (see 3S-6.1 for use of homo).

b) Cardanolides and bufanolides. The -olide ending of these names denotes the lactone grouping, and substituents must be named as prefixes.

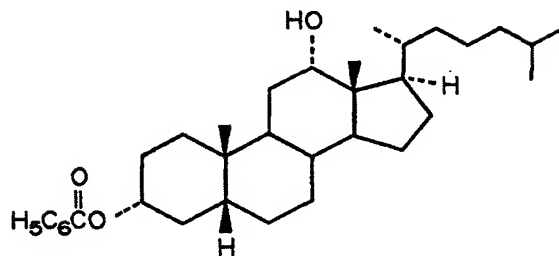
#### 3S-4.3. Esters of steroid alcohols

Esters of steroid alcohols are named by the appropriate steroid substituent group followed by that of the acyloxy group in its anionic form. The steroid name is formed by replacing the terminal -e of the hydrocarbon name by -yl, -diyl, etc. and inserting this before the locant with a Greek letter to designate position and configuration. When necessary locants should be used with the anionic part of the name. Examples:

5α-Cholestan-3β-yl acetate  
5β-Cholestane-3α,12α-diyl diacetate  
3-Oxoandrost-4-en-17β-yl acetate (trivial name testosterone acetate)  
17α-Hydroxy-20-oxopregn-5-en-3α-yl sulfate



(55)  
5β-Cholestane-3α,12α-diyl 12-acetate 3-benzoate



(56)

12 $\alpha$ -Hydroxy-5 $\beta$ -cholestan-3 $\alpha$ -yl benzoate

The prefix form acyloxy-, with the appropriate locants, is used if there is a preferred functional group as the suffix (e.g. an acid or lactone). Examples:

3 $\alpha$ -Acetoxy-5 $\beta$ -cardanolide3 $\alpha$ -Benzoyloxy-11 $\beta$ -hydroxy-20-oxo-5 $\beta$ -pregnan-21-oate (monobenzoate of 47)3 $\beta$ -Acetoxy-5 $\alpha$ -cholano-24,17-lactone (acetate of 52)

When the steroid acid has a trivial name that already specifies the hydroxyl group that is esterified, the prefix must be *O*-acyl-. Examples:

3-*O*-Acetylcholic acid17-*O*-Benzoyl estradiol-17 $\beta$ 3-*O*-Linolenoylcholesterol

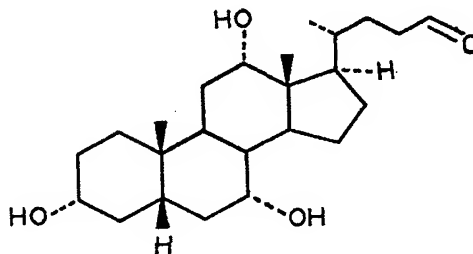
#### Notes

1) If it is wanted to emphasize the unesterified form of the steroid (e.g. in an index) the polyol may be named with the ester groups indicated as in the example 55 5 $\beta$ -cholestane-3 $\alpha$ ,12 $\alpha$ -diol 12-acetate 3-benzoate. This style was recommended in the previous edition of these recommendations, but does not follow standard systematic nomenclature rules [3].

2) In the case of simple sterols with trivial names, the substituent form of the trivial name may be used (e.g. cholesteryl linoleate). This form should not be used with polyols.

#### 3S-4.4. Oxo compounds

a) Aldehydes are named by using either the suffix -al (denotes change of  $-\text{CH}_3$  to  $-\text{CHO}$ , i.e. without change in the number of carbon atoms), or -aldehyde (denotes change of  $-\text{COOH}$  to  $-\text{CHO}$ , i.e. without change in the number of carbon atoms; the name is derived from that of the acid). The prefix oxo- denotes the change of  $\text{>CH}_2$  to  $\text{>CO}$ , thus also of  $-\text{CH}_3$  to  $-\text{CHO}$ , with no change in the number of carbon atoms. Examples:

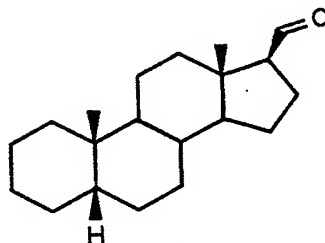
5 $\alpha$ -Androstan-19-al5 $\alpha$ -Cholan-24-al

(57)

3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -Trihydroxy-5 $\beta$ -cholan-24-al  
or cholaldehyde (from cholic acid)

If the aldehyde group is formed by substitution of a hydrogen atom in  $\text{>CH}$ ,  $\text{>CH}_2$  or  $-\text{CH}_3$  by  $-\text{CHO}$  i.e.  $\text{>C-CHO}$  the prefix formyl or suffix carbaldehyde is used. Examples:

3 $\beta$ -Formyl-5 $\alpha$ -cholan-24-oic acid



(58)

5β-Androstane-17β-carbaldehyde

b) For ketones, the suffix is *-one*, and the prefix *oxo-*. Examples:

5β-Androstan-3-one  
 Pregn-5-ene-3,20-dione  
 11-Oxo-5α-cholan-24-oic acid

#### Notes

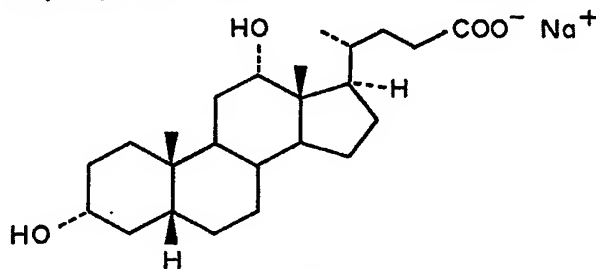
1) The prefix *oxo-* should also be used in connection with generic terms, e.g. 17-oxo steroids. The term "17-keto steroids", often used in the medical literature, is incorrect because C-17 is specified twice, as the term *keto* denotes C=O.

2) Many steroids carry hydroxyl groups as well as oxo groups. In this case, the suffix *-one* must be used, and hydroxyl groups indicated by prefixes, unless the compounds have trivial names (see Table 2). If the principal functional group (and hence the suffix) is preferred to either hydroxyl or oxo groups both hydroxyl and oxo groups are indicated as prefixes.

#### 3S-4.5. Alcohols

Alcohols are named with the suffix *-ol* or the prefix *hydroxy-*, with the appropriate locants. Examples:

5β-Cholestane-3α,11β-diol  
 3α-Hydroxy-5α-androstan-17-one (trivial name: androsterone)



(59)

Sodium 3α,12α-dihydroxy-5β-cholan-24-oate  
 common name: sodium 7-deoxycholate

#### Notes

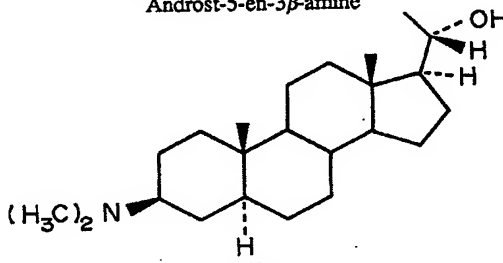
1) Composite suffixes *-olone* and *-onol*, to denote simultaneous presence of hydroxyl and ketonic groups, are not permitted by IUPAC Recommendations [3] and should not be used.

2) A few trivial names exist for hydroxy ketones (see Table 2).

#### 3S-4.6. Amines

Amines are named by means of the suffix *-amine* or the prefix *amino-*. Examples:

Androst-5-en-3β-amine



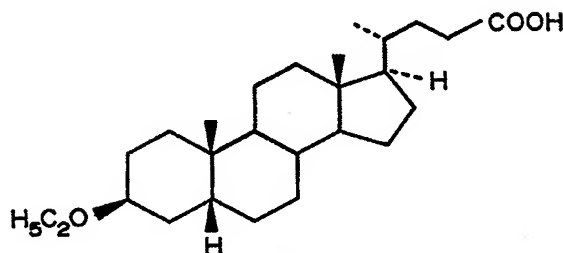
(60)

(20S)-3β-(Dimethylamino)-5α-pregnan-20-ol

3S-4.7. *Ethers*

Ethers are named as alkoxy derivatives. Examples:

17 $\beta$ -Methoxyandrost-4-en-3-one



(61)

3 $\beta$ -Ethoxy-5 $\beta$ -cholan-24-oic acid

Ethers and partial ethers of steroid polyols are named either by using the alkoxy- prefix, or by the prefix *O*-alkyl- if the hydroxy group etherified is already specified in a trivial name. Examples:

(20*S*)-3 $\beta$ ,17,20-Trimethoxy-5 $\alpha$ -pregnane

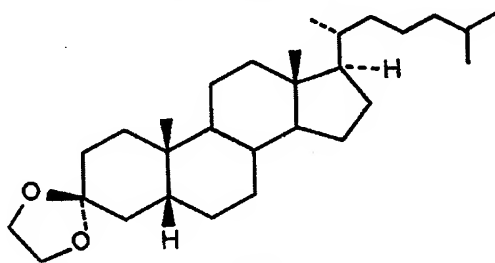
(20*S*)-3 $\beta$ ,17-Dimethoxy-5 $\alpha$ -pregnan-20-ol

21-*O*-Methylcortisol

3S-4.8. *Acetals and ketals*

Acetals and ketals of oxo steroids are named as dialkoxy steroids. Examples:

3,3-Dimethoxycholest-4-ene



(62)

3,3-(Ethylenedioxy)-5 $\beta$ -cholestane

Similarly, acetals formed by an oxo compound reacting with two hydroxyl groups of a steroid may be named alkylenedioxy compounds. Example:

2 $\alpha$ ,3 $\alpha$ -(Methylenedioxy)pregn-5-ene (see 101)

3S-4.9. *Trivial names of important steroids*

Examples of trivial names retained for important steroid derivatives, these being mostly natural compounds of significant biological activity, are given in Table 2.

**Note** If these trivial names are used as a basis for naming derivatives or stereoisomers, the derived trivial name must make the nature of the modification completely clear and is preferably accompanied at first mention by the full systematic name. For example, in steroid papers *epi* is often used with trivial names to denote inversion at one centre; the name 11-*epi*cortisol defines the compound fully since cortisol is already defined as the 11 $\beta$ -alcohol; but the name *epi*cortisol does not define the compound and is inadequate.

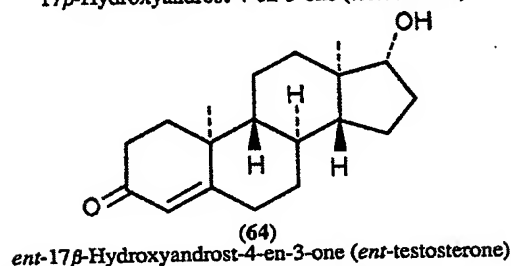
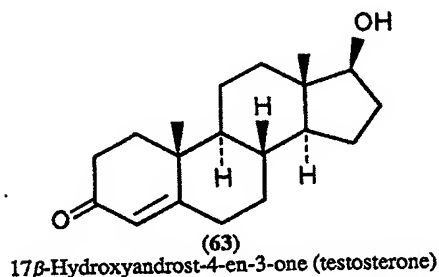
3S-4.10. *Use of international non-proprietary names*

International non-proprietary names (INNs) have been given to many steroids of pharmaceutical importance [6]. For convenience, a selection of some of these names is given in the appendix. If these names are used in biochemical papers, it is recommended that once in the paper, e.g. in a footnote or under Materials and Methods, the full systematic name is also given. International non-proprietary names should not be used as a basis for the names of modified compounds.

3S-5. **STEREOCHEMICAL MODIFICATIONS**3S-5.1. *Use of the prefix ent-*

If, as for instance in a synthetic compound, there is stereochemical inversion at all the asymmetric centres whose configurations need not be specified in a name, the italicized prefix *ent-* (a contracted form of *enantio-*) is placed in front of the complete name of the compound. This prefix denotes inversion at all asymmetric centres (including those due to named substituents) whether these are cited separately or are implied in the name.

Examples:



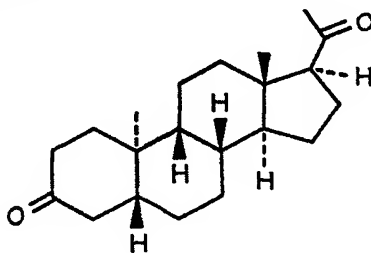
*Note* When numerals are used to enumerate formulae, the prefix *ent*- may be used to indicate the enantiomer. Thus, e.g. compound 64 above may be designated *ent*-63.

Table 2. Trivial names of some important steroid derivatives

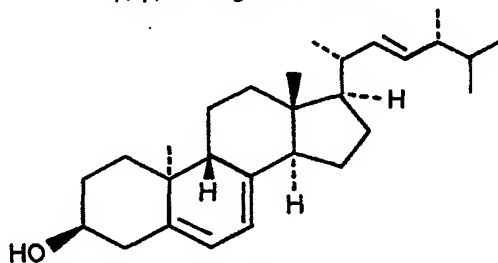
Trivial name	Systematic steroid name
Aldosterone	18,11-hemiacetal of 11 $\beta$ ,21-dihydroxy-3,20-dioxopregn-4-en-18-al or 11 $\beta$ ,18-epoxy-18 $\xi$ -hydroxypregn-4-ene-3,20-dione
Androsterone	3 $\alpha$ -hydroxy-5 $\alpha$ -androst-17-one
Brassinolide	(22 <i>R</i> ,23 <i>R</i> )-2 $\alpha$ ,3 $\alpha$ ,22,23-tetrahydroxy-6,7-seco-5 $\alpha$ -campestano-6,7-lactone
Calcidiol (93)	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-5,7,10(19)-triene-3,25-diol
Calciol (92) = cholecalciferol	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-5,7,10(19)-trien-3-ol
Calcitriol (94)	(5 <i>Z</i> ,7 <i>E</i> )-(1 <i>S</i> ,3 <i>R</i> )-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol
Cholesterol	cholest-5-en-3 $\beta$ -ol
Cholic acid	3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxy-5 $\beta$ -cholan-24-oic acid
Corticosterone	11 $\beta$ ,21-dihydroxypregn-4-ene-3,20-dione
Cortisol	11 $\beta$ ,17,21-trihydroxypregn-4-ene-3,20-dione
Cortisol acetate	21- <i>O</i> -acetylcortisol
Cortisone	17,21-dihydroxypregn-4-ene-3,11,20-trione
Cortisone acetate	21- <i>O</i> -acetylcortisone
Deoxycorticosterone	21-hydroxypregn-4-ene-3,20-dione (i.e. the 11-deoxy derivative of corticosterone)
Ecdysone	(22 <i>R</i> )-2 $\beta$ ,3 $\beta$ ,14 $\alpha$ ,22,25-pentahydroxy-5 $\beta$ -cholest-7-en-6-one
Ercalciol = ergocalciferol	(5 <i>Z</i> ,7 <i>E</i> ,22 <i>E</i> )-(3 <i>S</i> )-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol
Ergosterol (7)	(22 <i>E</i> )-ergosta-5,7,22-trien-3 $\beta$ -ol
Estradiol-17 $\alpha$	estra-1,3,5(10)-triene-3,17 $\alpha$ -diol
Estradiol-17 $\beta$	estra-1,3,5(10)-triene-3,17 $\beta$ -diol
Estriol	estra-1,3,5(10)-triene-3,16 $\alpha$ ,17 $\beta$ -triol
Estrone	3-hydroxyestra-1,3,5(10)-trien-17-one
Lanosterol	lanosta-8,24-dien-3 $\beta$ -ol
Lithocholic acid	3 $\alpha$ -hydroxy-5 $\beta$ -cholan-24-oic acid
Progesterone	pregn-4-ene-3,20-dione
Pseudotigogenin	(25 <i>R</i> )-5 $\alpha$ -furost-20(22)-ene-3 $\beta$ ,26-diol
Sarsapogenin	(25 <i>S</i> )-5 $\beta$ -spirostan-3 $\beta$ -ol
Smilagenin	(25 <i>R</i> )-5 $\beta$ -spirostan-3 $\beta$ -ol
Testosterone (63)	17 $\beta$ -hydroxyandrost-4-en-3-one
Tigogenin	(25 <i>R</i> )-5 $\alpha$ -spirostan-3 $\beta$ -ol

3S-5.2. Use of  $\alpha$  and  $\beta$  for bridgeheads

If there is stereochemical inversion at not more than half of the asymmetric centres whose configurations need not be specified in a name, the configurations of the hydrogen atoms or substituents at the affected bridgeheads, or the carbon chain (if any) at position 17, are stated by means of a prefix or prefixes  $\alpha$  or  $\beta$ , each with its appropriate locant, placed before the stem name laid down in 3S-2 and 3S-3. Examples:



(65)  
5 $\beta$ ,9 $\beta$ ,10 $\alpha$ -Pregnane-3,20-dione



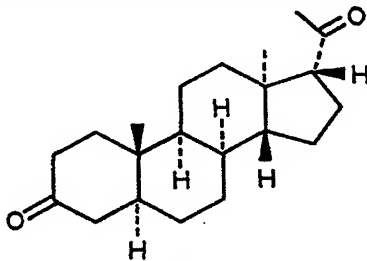
(66)  
(22*E*)-9 $\beta$ ,10 $\alpha$ -Ergosta-5,7,22-trien-3 $\beta$ -ol  
trivial name: lumisterol

*Note* The prefix *retro*, indicating 9 $\beta$ ,10 $\alpha$  configuration, should not be used.

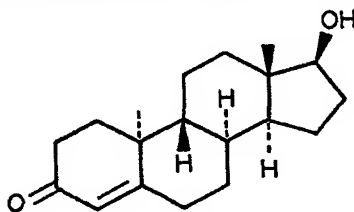
3S-5.3. Use of  $\alpha/\beta$  and *ent*-

The enantiomer of a compound designated as in Recommendation 3S-5.2 is given the same name preceded by *ent*.

*Note* This Recommendation covers the compounds in which there is inversion at a majority, but not all, of the asymmetric centres that need not be specified in the name. Examples:



(67)  
*ent*-5 $\beta$ ,9 $\beta$ ,10 $\alpha$ -Pregnane-3,20-dione  
(not 5 $\alpha$ ,8 $\alpha$ ,13 $\alpha$ ,14 $\beta$ ,17 $\alpha$ -pregnane-3,20-dione)



(68)  
*ent*-17 $\alpha$ -Hydroxy-13 $\alpha$ ,14 $\beta$ -androst-4-en-3-one  
(not 17 $\beta$ -hydroxy-8 $\alpha$ ,9 $\beta$ ,10 $\alpha$ -androst-4-en-3-one)

3S-5.4. Use of the prefix *rac*-

Racemates, as for instance obtained by synthesis, are named by use of an italicized prefix *rac*- (an abbreviation of *racemo*-), placed before the complete name of the compound, the enantiomer chosen for naming being that required by Recommendations 3S-5.1 to 3S-5.3.

Example: A racemate composed of compounds 63 and 64 (= *ent*-63) is named *rac*-17 $\beta$ -hydroxyandrost-4-en-3-one or *rac*-testosterone.

**Note** The designation of  $\alpha$  and  $\beta$  to the substituents refers to the normal series, not to the *ent*-series; the prefix *ent*- indicates that their absolute spatial orientation is inverted.

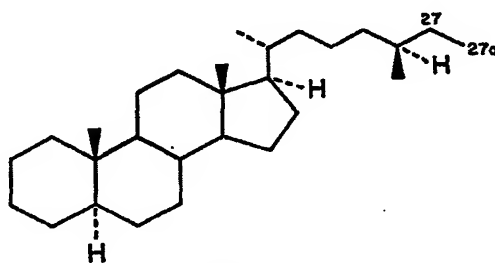
 $\Delta$  3S-5.5. Use of *R*\* and *S*\*

When the relative, but not the absolute, configuration of two or more asymmetric centres in a steroid derivative is known, this may be indicated by *R*\* or *S*\* according to Recommendations E-4.10 and F-6.7 of [3].

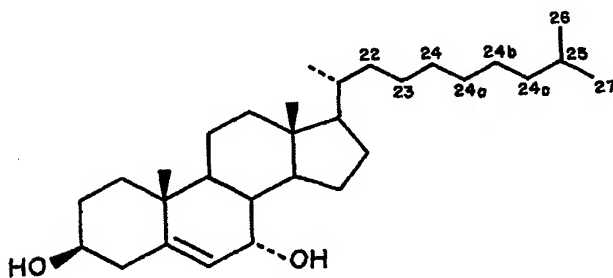
## 3S-6. LENGTHENING AND SHORTENING OF SIDE CHAINS AND ELIMINATION OF METHYL GROUPS

3S-6.1. Use of the prefix *homo*-

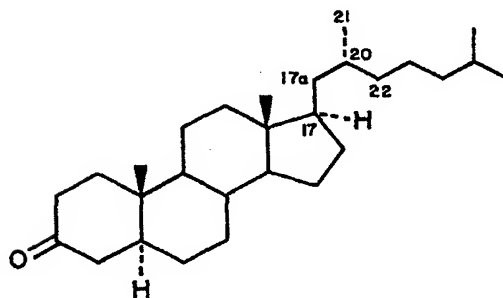
Lengthening of a side chain by insertion of one (or more) methylene groups is indicated by the prefix *homo*- (*dihomo*- etc.). The prefix is preceded by the (complex) locant(s) of the carbon atom(s) inserted. Examples:



(69)  
(25*R*)-27a-Homo-5 $\alpha$ -cholestane



(70)  
24a,24b,24c-Trihomocholest-5-ene-3 $\beta$ ,7 $\alpha$ -diol



(71)  
17(20)a-Homo-5 $\alpha$ -cholestan-3-one

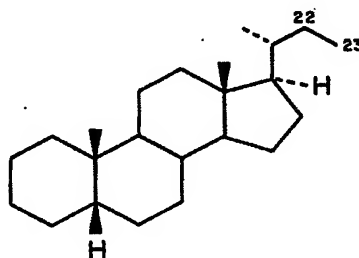
*Notes*

1) If the methylene group is inserted into a methyl C-H bond or next to a methylene group the letter a (b etc.) is added to the locant of the highest numbered atom (e.g. example 69 is 27a-homo- not 26a-homo-).

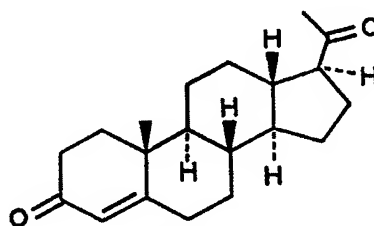
2) If the methylene group is inserted between two side-chain branch points that are directly linked, or between C-17 and a branch point at C-20 (i.e. Table 1 except pregnane) both locants are used with the letter a (b etc.) and the higher numbered locant in parenthesis. The higher number may be omitted in a structural formula but must be used in the name of the homo-steroid (e.g. 17a in compound 71).

**3S-6.2. Use of the prefix *nor*-**

Elimination of a methylene group ( $-\text{CH}_2-$ ) from a steroid side chain is indicated by the prefix *nor*-, which in all cases is preceded by the number of the carbon atom that disappears. When alternatives are possible, the number attached to *nor*- is the highest permissible. Elimination of two methylene groups is indicated by the prefix *dinor*-. The remainder of the original steroid numbering is retained (see 73). Examples:



(72)  
24-Nor-5 $\beta$ -cholane

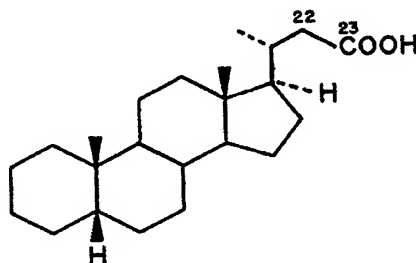


(73)  
18-Norpregn-4-ene-3,20-dione

Exceptions: By recommendations 3S-2.1 and 3S-2.2 the names gonane (for 18,19-dinorandrostane) and estrane (for 19-norandrostane) constitute exceptions to the above Recommendation 3S-6.2. The names gonane and estrane are used also as parent names for their derivatives.

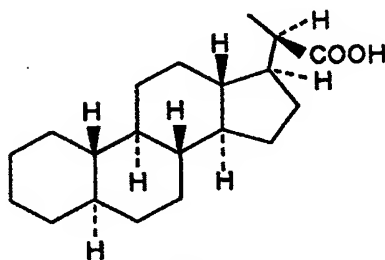
However, 18-*nor*- and 19-*nor*- are used with other parent and trivial names, as in 19-norpregnane, 18,19-dinor-spirostan, and 18-norestrone.

The compound produced by shortening the side chain of pregnane is named 17 $\beta$ -methylandrostane rather than 21-norpregnane. See also Recommendation 3S-6.3. Examples:



(74)  
24-Nor-5 $\beta$ -cholan-23-oic acid





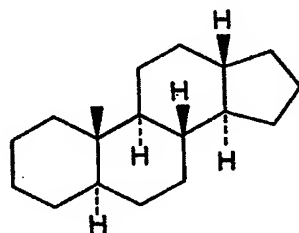
(75)  
(20R)-18,19-Dinor-5 $\alpha$ -pregnane-20-carboxylic acid  
(not 18,19,23,24-tetranor-5 $\alpha$ -cholan-21-oic acid)

▲ 3S-6.3. *Preference between homo- and nor-*

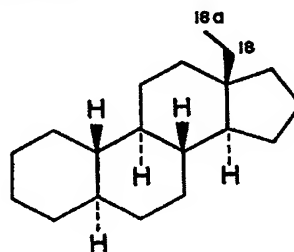
A compound with a skeleton that differs from the fundamental parent systems (see 3S-2.1 to 3S-2.4 and 3S-3.1 to 3S-3.4) by changes in the side chain(s) can often be named by several different methods involving either side chain lengthening (3S-6.1) or shortening (3S-6.2) and/or alkylation (3S-4.0) and/or addition of carbon atoms associated with a functional group [3S-4.1(b), 3S-4.2(a), 3S-4.4(a)]. The preferred name is selected by the following recommendations applied in order:

a) A name should be derived by the fewest number of modifications of the fundamental parent system. Both detachable (e.g. alkyl) and non-detachable (e.g. homo or nor) prefixes are considered as modifications. Dihomo, dinor, etc., are counted as two modifications each.

b) Non-detachable prefixes are preferred to detachable prefixes. Examples:



(76)  
18-Nor-5 $\alpha$ -androstane  
(not 10-methyl-5 $\alpha$ -gonane)



(77)  
18 $\alpha$ -Homo-5 $\alpha$ -estrane  
(not 13-ethyl-5 $\alpha$ -gonane or  
13-ethyl-18-nor-5 $\alpha$ -estrane)

*Notes*

1) As an exception to recommendation (b) above, 17 $\beta$ -methyl-5 $\alpha$ -androstane is preferred to 21-nor-5 $\alpha$ -pregnane and 5 $\alpha$ -androstane-17 $\beta$ -carboxylic acid is preferred to 21-nor-5 $\alpha$ -pregnan-20-oic acid.

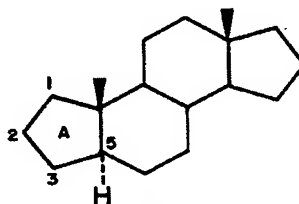
2) Compound 77 is 13-ethyl-18-nor-5 $\alpha$ -estrane in current Chemical Abstracts Service index nomenclature.

3S-7. RING CONTRACTION AND EXPANSION

3S-7.1. *Use of the prefix nor-*

Ring contraction by loss of an unsubstituted methylene group is indicated by the prefix nor-. For loss of two methylene groups, dinor- is used. The methylene group(s) lost is considered to include the highest numbered unsubstituted atom of the ring involved, and the locant of that lost methylene group precedes the prefix nor- in the nor-compound. The remainder of the original numbering is retained. Example:

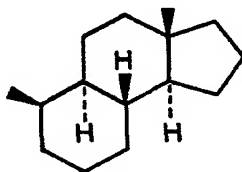
In 4-nor-5 $\alpha$ -androstane (78) C-4 is missing.



(78)

3S-7.2. Use of the prefix *des-*

The removal of a terminal ring, with addition of a hydrogen atom at each junction atom with the adjacent ring, is indicated by the prefix *des-*, followed by the italic capital letter designating that ring (3S-1.1); substituents and stereochemistry implied in the trivial name remain unless otherwise stated. Example:



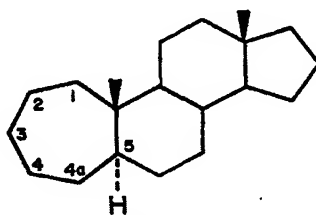
(79)  
Des-A-androstane

**Note** The prefix *des-* is used here, not *de-*, because of the ease of confusing *de-* with the letter D in speech.

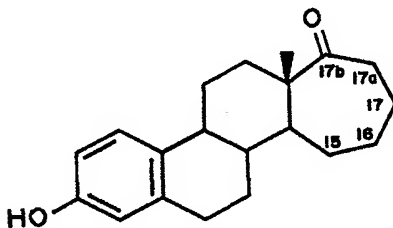
3S-7.3. Use of the prefix *homo-*

Ring expansion by inclusion of one methylene group is indicated by the prefix *homo-*, by two methylene groups by *dihomo-*. The prefix is preceded by the (complex) locant(s) of the carbon atom(s) inserted. These are chosen in the following way:

a) If the methylene group is not inserted between directly linked bridgeheads or between C-13 and C-17 carrying a side chain, the letter a, b etc. is added to the locant of the highest numbered atom of the ring that is not a bridgehead. Examples:

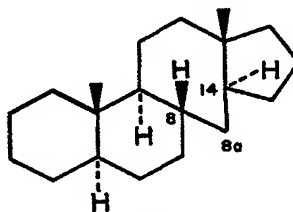


(80)  
4a-Homo-5 $\alpha$ -androstane

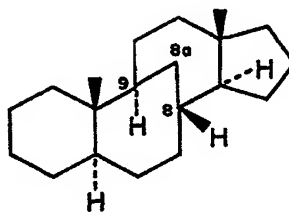


(81)  
3-Hydroxy-17a,17b-dihomoestra-1,3,5(10)-trien-17b-one

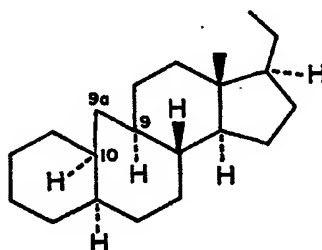
b) If the methylene group is inserted between directly linked bridgeheads or between C-13 and C-17 carrying a side chain, the letter a (or a and b) is added to the pair of locants indicating the atoms on either side, and the higher numbered locant is placed in parentheses. Examples:



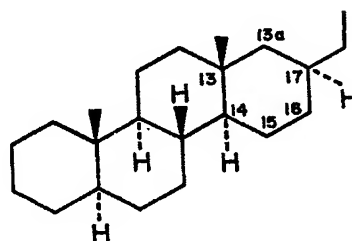
(82)  
8(14)a-Homo-5 $\alpha$ -androstane



(83)  
8(9)α-Homo-5α-androstane



(84)  
9(10)α-Homo-19-nor-5α,10α(H)-pregnane



(85)  
13(17)α-Homo-5α-pregnane

The locant(s) with the prefix homo- is placed after the prefixes required for functional groups (cf. 3S-4), before the stereodescriptor (e.g. 5β) of the stem name, or if such is not required, directly before the stem name.

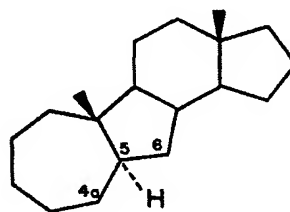
#### Notes

- △ 1) Recommendation 3S-7.3 deviates from the former convention in 2S-8; the present recommendation is in line with the general Recommendation F-4.5 (cf. Section F in [3]).

2) Although complex locants are necessary in the names of homo-steroids, simple locants may be used with structural formulae, e.g. 8a in compound 82 or 13a in compound 85 with the lower-numbered carbon atom as parent locant.

#### 3S-7.4. Use of both nor- and homo- in one name

The above recommendations for ring expansion and contraction may be used for modifications of two rings in the same molecule, as illustrated in example 86.



(86)  
4a-Homo-7-nor-5α-androstane

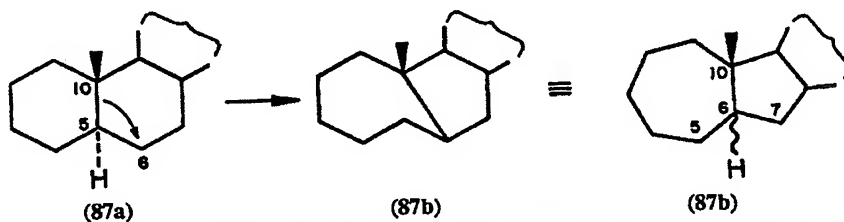
## Notes

1) Names incorporating homo- and nor- are normally preferred to alternatives incorporating cyclo- and seco- (cf. examples 84 and 86).

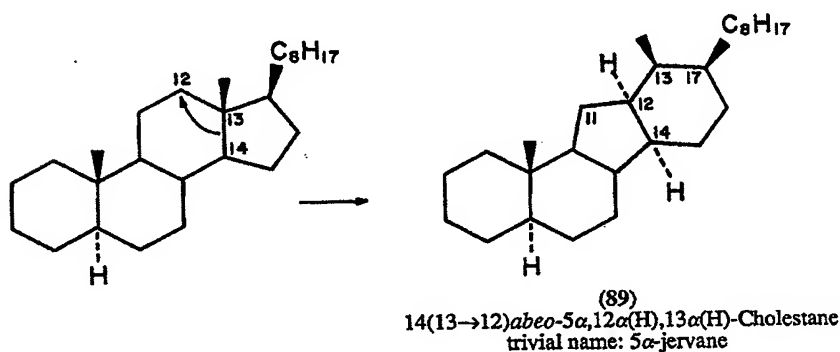
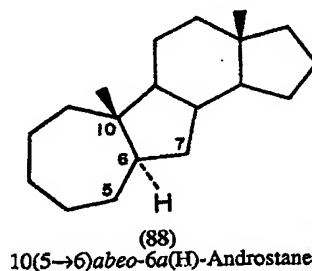
2) A compound with excessive modification of the steroid skeleton usually is best described by a systematic name. It is recommended that no more than two of the steroid rings be altered by any combination of the prefixes homo- and nor-.

## 3S-7.5. Use of the prefix abeo-

As an alternative to the application of nor- and homo- to the same molecule, the abeo system may sometimes be used. A compound that may be considered to arise from a steroid by bond migration may be given the name laid down in the preceding Recommendations for the steroid in question, to which is attached a prefix of the form  $x(y \rightarrow z)$ abeo-. This prefix is compiled as follows: a numeral denoting the stationary (unchanged) end of the migrating bond ( $x$ ) is followed by parentheses enclosing (i) the number denoting the original position ( $y$ ) from which the other end of this bond has migrated, (ii) an arrow, and (iii) the number ( $z$ ) denoting the new position to which the bond has moved (see formulae 87a and 87b).



The original numbering is retained for the new compound and is used for the numbers  $x$ ,  $y$  and  $z$ . It is always necessary to specify the resulting stereochemistry. Examples:



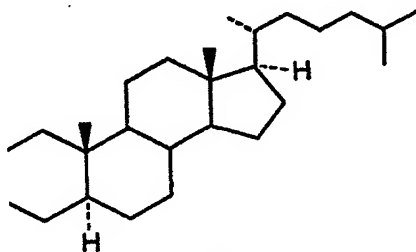
## Notes

1) The abeo nomenclature described in this Recommendation is permissive, not compulsory. It is most suitable for use in discussions of reaction mechanism and biogenesis. For registration in a general (non-steroidal) compendium, the general systematic names, or names assigned by the homo- or nor- method, may be preferable. Thus 88 is identical with 86.

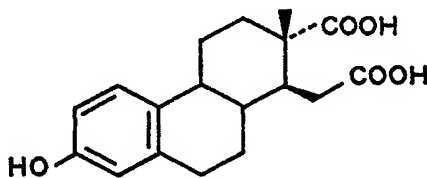
2) The abeo system has the advantage that the normal numbering of the steroid skeleton is retained. An example is 89, the parent structure of some steroid alkaloids. Also, 84 may be named 9(10→19)abeo-5a,10a(H)-pregnane, C-9a remaining C-19.

**3S-8 RING FISSION****3S-8.1. Use of the prefix *seco*-**

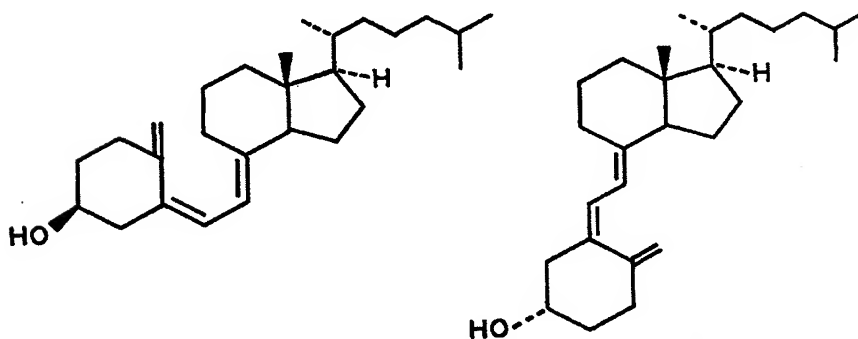
Fission of a ring, with addition of a hydrogen atom at each terminal group thus created, is indicated by the prefix *seco*-, the original steroid numbering being retained. (If more than one ring is opened, general systematic nomenclature may be preferable. The principles of Note 2 to Recommendation 3S-7.4 apply also to *seco*-steroids.) Examples:



(90)  
2,3-Seco-5 $\alpha$ -cholestane



(91)  
3-Hydroxy-16,17-secoestra-1,3,5(10)-triene-16,17-dioic acid



(92a) (92b)  
(5Z,7E)-(3S)-9,10-Secocholesta-5,7,10(19)-trien-3-ol  
trivial name: cholecalciferol or calciol

▲ **3S-8.2. Use of  $\alpha$  and  $\beta$  in *seco*-compounds**

The stereochemical steroid descriptors  $\alpha$  and  $\beta$  apply only when the remaining rings of a *seco*-compound are oriented as in the parent steroid, but not to alternative conformations (see formulae 92a and 92b). It is therefore recommended that after fission of ring B the stereochemistry of substituents on ring A is indicated by the *R,S* convention and  $\alpha$  and  $\beta$  are restricted to rings C and D. Likewise after fission of ring C the stereochemistry of substituents on ring D is indicated by the *R,S* convention and  $\alpha$  and  $\beta$  are restricted to rings A and B.

▲ **3S-9. VITAMIN D GROUP**

**3S-9.0. General**

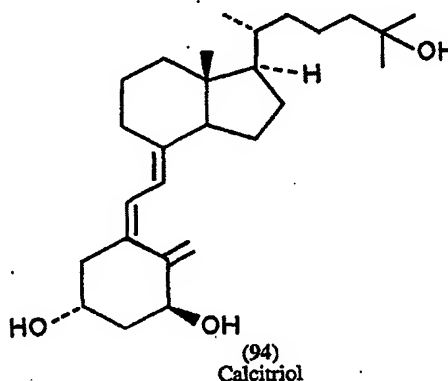
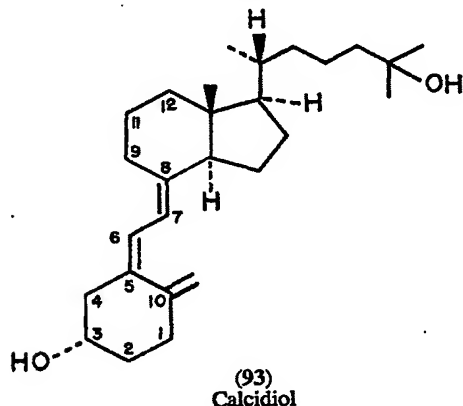
By far the most important *seco*-steroids are the D vitamins and their derivatives. They can be named according to Recommendation 3S-8.1, but this results in very cumbersome names. For this reason and for the benefit of biochemists, a set of trivial names has been proposed [5], which can also be used as stem names for modified compounds. These names are permissive, not compulsory; authors may prefer to use the systematic *seco*-steroid names, which may indeed be more convenient for complicated structures.

Another reason for the revision of the vitamin D nomenclature is the confusion arising from the application of the steroid descriptors  $\alpha$  and  $\beta$ . According to 3S-8.2, the  $R,S$  system should be used to describe the stereochemistry of substituents in ring A. Likewise, the geometry of the double bonds should be assigned by the  $E,Z$  system.

The names of the principal members of the vitamin D group are given in Table 3.

### 3S-9.1. Trivial names

The compound 92, also known as vitamin D<sub>3</sub> or cholecalciferol, is named calcidiol. The name implies the stereochemistry shown, which is 3*S*,5*Z*,7*E*. The name should only be used for the compound with a hydroxyl group at C-3 with the same orientation as in 3 $\beta$ -hydroxy steroids. Compound 93 is named calcidiol, and compound 94 is calcitriol. Some more trivial names are listed in Table 3, together with the systematic steroid names.



### Notes

1) The names calcidiol, calcitriol, calcitriol imply not only the stereochemistry but also the location of the hydroxyl group(s). Compounds with hydroxyl groups in other positions must be named either according to 3S-9.4 (below), or in the usual semisystematic way applying Recommendation 3S-8.1.

2) The trivial names cholecalciferol and ergocalciferol are retained. They should, however, not be used for naming metabolites.

3) Because of the nature of the sequence rule, it is not possible to transfer  $R$  or  $S$  from one compound to its derivatives. Calcidiol is a 3*S* compound but calcitriol is a 3*R* compound though the absolute configuration of the hydroxyl group at C-3 is not changed.

Table 3. Nomenclature for vitamin D compounds

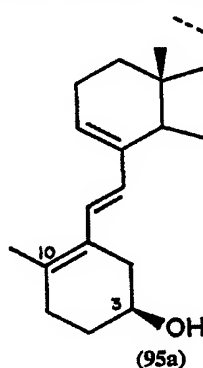
Current trivial name	Recommended trivial name	Systematic steroid name
Cholecalciferol	calcidiol or cholecalciferol (92)	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-5,7,10(19)-trien-3-ol
25-Hydroxycholecalciferol	calcidiol (93)	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-5,7,10(19)-triene-3,25-diol
1 $\alpha$ ,25-Dihydroxycholecalciferol	calcitriol (94)	(5 <i>Z</i> ,7 <i>E</i> )-(1 <i>S</i> ,3 <i>R</i> )-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol
Ergocalciferol	ercalcidiol or ergocalciferol	(5 <i>Z</i> ,7 <i>E</i> ,22 <i>E</i> )-(3 <i>S</i> )-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol <sup>a</sup>
1 $\alpha$ ,25-Dihydroxyergocalciferol	ercalcitriol	(5 <i>Z</i> ,7 <i>E</i> ,22 <i>E</i> )-(1 <i>S</i> ,3 <i>S</i> )-9,10-secoergosta-5,7,10(19),22-tetraen-1,3,25-triol <sup>b</sup>
22,23-dihydroergocalciferol	(24 <i>S</i> )-methylcalcidiol or 22,23-dihydroercalcidiol	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secoergosta-5,7,10(19)-trien-3-ol <sup>b</sup>
1 $\alpha$ ,24 <i>R</i> ,25-Trihydroxycholecalciferol	calcitriol	(5 <i>Z</i> ,7 <i>E</i> )-(1 <i>S</i> ,3 <i>S</i> ,24 <i>R</i> )-9,10-secocholesta-5,7,10(19)-triene-1,3,24,25-tetrol
Previtamin D <sub>3</sub>	(6 <i>Z</i> )-tacalcidiol	(6 <i>Z</i> )-(3 <i>S</i> )-9,10-secocholesta-5(10),6,8-trien-3-ol
Tachysterol <sub>3</sub>	tacalcidiol (95)	(6 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-5(10),6,8-trien-3-ol
Dihydrotachysterol <sub>3</sub>	dihydrocalcidiol	(5 <i>Z</i> ,7 <i>E</i> )-(3 <i>S</i> ,10 <i>S</i> )-9,10-secocholesta-5,7-dien-3-ol
Isovitamin D <sub>3</sub>	(5 <i>E</i> )-isocalcidiol (96)	(5 <i>E</i> ,7 <i>E</i> )-(3 <i>S</i> )-9,10-secocholesta-1(10),5,7-trien-3-ol

<sup>a</sup> 24*R*-configuration

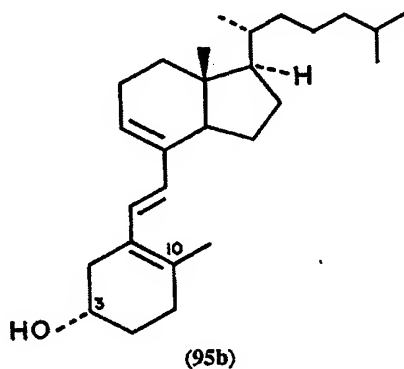
<sup>b</sup> 24*S*-configuration

3S-9.2. *Modifications of the triene system*

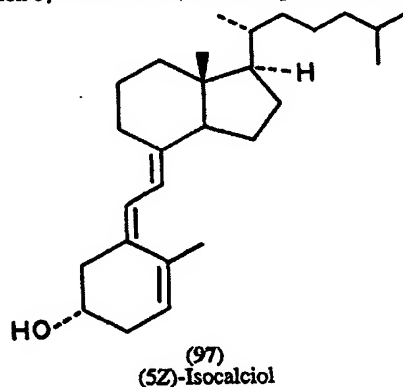
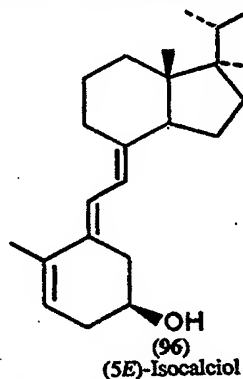
The prefix *ta-* (derived from tachysterol) indicates a change of the triene system from (5Z,7E)-5,7,10(19) to (6E)-5(10),6,8 as in tacalcioi 95a and 95b.



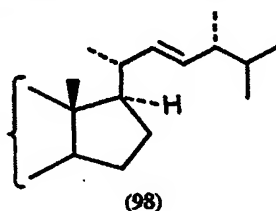
Tacalcioi



The prefix *iso-* (derived from isovitamin D) when applied to calcioi changes the location of the triene system to 1(10),5,7 with 7E configuration implied; the geometry at position 5, when known, must be specified by 5E 96 or 5Z 97.

3S-9.3. *Modification of the side chain*

The prefix *er-* (derived from ergosterol) is used to indicate the side chain of the vitamin D<sub>2</sub> or ergocalciferol. This prefix implies the 22E,24R configuration as given in formula 98 unless otherwise specified.

3S-9.4. *Additional hydroxyl groups*

Additional hydroxyl groups cannot be indicated by modification of the suffix -ol, -diol, -triol, -tetrol, since these have definite meanings (see Table 3). They can, however, be added as prefix, e.g. (1S)-1-hydroxycalcioi, 16 $\beta$ -hydroxycalcioi. If possible, the full stereochemistry should be given, e.g. (25R)-26-hydroxycalcioi. For other modifications and more detailed discussion of the nomenclature problems in the vitamin D field, the reader is referred to the original document [5].

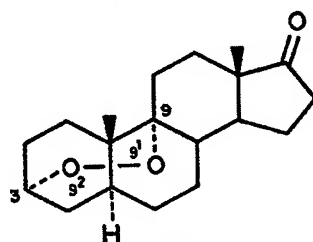
3S-10. **ADDITIONAL RINGS**3S-10.0. *General*

When additional rings are formed within, or on, a steroid nucleus, it is often desirable to retain the steroid stem name, since it implies the stereochemistry of most of the chiral centres. The following recommendations show how such names can be constructed. It will be seen, however, that these names may become cumbersome with more complicated - especially substituted - structures. Recourse to general systematic nomenclature may then be preferable.

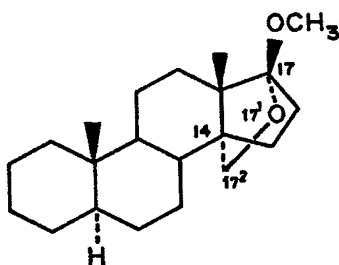
The decision whether any one compound shall receive such a modified steroid name or a general systematic name is left to authors and editors in the particular circumstances of each case. Moreover, the requirements of different journals or compendia are not necessarily identical.

### 3S-10.1. Bridged steroids

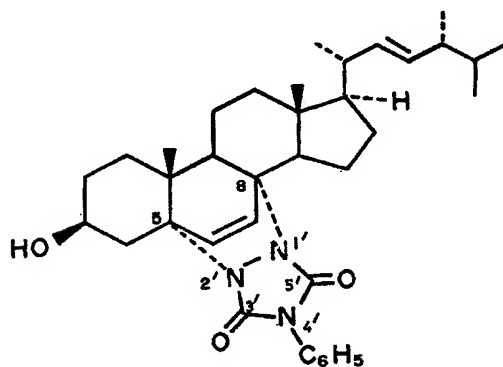
Steroids with non-adjacent ring positions linked by a bivalent bridge such as -O-O-,  $-\text{[CH}_2\text{]}_n-$  (see recommendations A-34 and B-15 in [3]) are named by the appropriate name and locants to indicate its attachment and  $\alpha$  or  $\beta$  to indicate stereochemistry where necessary. Examples:



(99)  
3 $\alpha$ ,9-Epidioxy-5 $\alpha$ -androstan-17-one



(100)  
17 $\beta$ -Methoxy-17 $\alpha$ ,14-(epoxymethano)-5 $\alpha$ -androstane



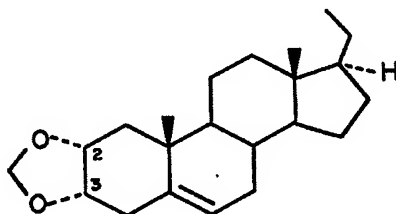
(101)  
(22E)-3 $\beta$ -Hydroxy-4'-phenyl-5,8-[1,2]epi[1,2,4]triazolo-5 $\alpha$ ,8 $\alpha$ -ergosta-6,22-diene-3',5'-dione

#### Notes

- 1) In a composite bridge such as epoxymethano in compound 100 the first number of the two locants cited in front of the bridge corresponds to the first cited component of the composite bridge i.e. epoxy (recommendation B-15.2 in [3]).
- 2) With linear bridges such as in compounds 99 and 100 the atoms may be labelled for identification by the superscript number starting from the higher numbered attachment position (see 3S-2.7). It is not recommended that the steroid numbering should be continued with the bridge atoms as the highest used number depends on the steroid skeleton present (recommendation A-34.2 in [3]).
- 3) With a cyclic bridge, such as in compound 101, the numbering of the ring system is retained but each number is primed if needed for identification or further substitution. The name of the bridge includes the attachment positions in front of the name. These locants and any required to name the ring are cited within square brackets without any primes (ref. 3, recommendation B-3.1). Low numbers are preferred for the attachment positions with the lower number nearer the higher numbered attachment position of the steroid.



This system should not normally be extended to adjacent positions, except for simple symmetric bridges, e.g. 102. For other cases see 3S-10.2. Example:

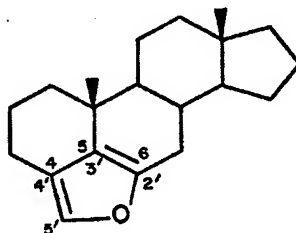


(102)

2 $\alpha$ ,3 $\alpha$ -(Methylenedioxy)pregn-5-ene

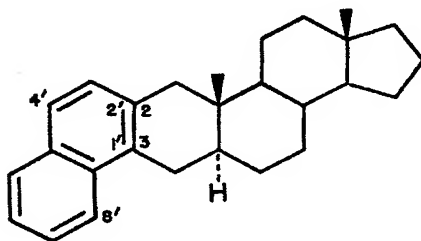
### 3S-10.2. Additional ring(s) fused to a steroid

Fusion of a carbocyclic or heterocyclic ring component with the maximum number of non-cumulative double bonds to a steroid may be indicated by a modification of fusion nomenclature (see recommendations A-21.3 to A-21.6, B-3.1 to B-3.3 in [3]). The preferred component is always the steroid. The name of the carbocyclic or heterocyclic attached component is modified to give its prefix form and is cited in front of the steroid name with the nature of the fusion indicated between square brackets. The numbering of the steroid moiety is retained; the atoms of the attached component are identified by primed locants. Those involved in fusion are cited in the order corresponding to those of the steroid. Examples:

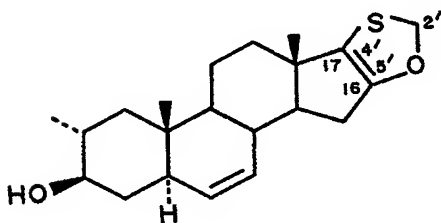


(103)

Furo[4',3',2':4,5,6]androstane



(104)

Naphtho[2',1':2,3]-5 $\alpha$ -androstane

(105)

2 $\alpha$ -Methyl[1,3]oxathiolo[5',4':16,17]-5 $\alpha$ -androst-6-en-3 $\beta$ -ol

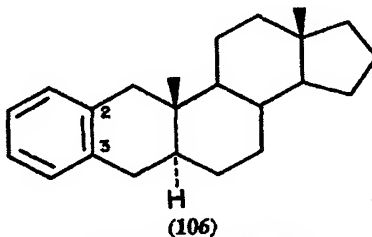
## ▲ Notes

1) There are three changes from the previous recommendations [1], that are still used by Chemical Abstracts Service index nomenclature:

- (i) the unsaturation in the steroid ring due to the fused component is not cited;
- (ii) the preferred component is always the steroid;
- (iii) a terminal a or o of the prefix is not elided.

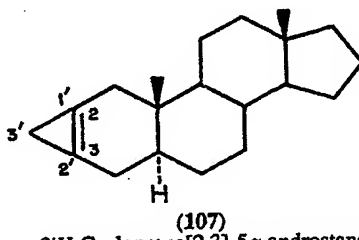
2) The current Chemical Abstracts Service index names for 103, 104 and 105 are androst-5-eno[6,5,4-*bc*]furan, naphth[2',1':2,3]-5 $\alpha$ -androst-2-ene, and 2 $\alpha$ -methyl-5 $\alpha$ -androsta-6,16-dieno[17,16-*d*][1,3]oxathiol-3 $\beta$ -ol respectively.

Fusion locants may be omitted if unnecessary. Example:

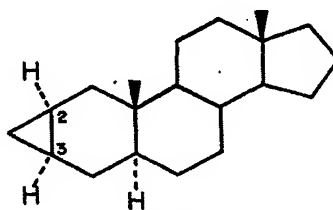


Benzo[2,3]-5 $\alpha$ -androstane

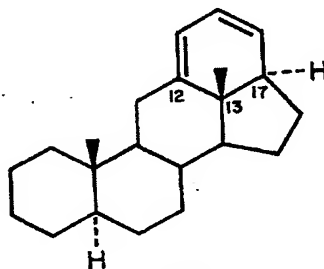
If necessary isomers are distinguished by the use of indicated hydrogen (see recommendation A-21.6 in [3]). If there is a choice of locants due to fusion the unprimed locant is used. Examples:



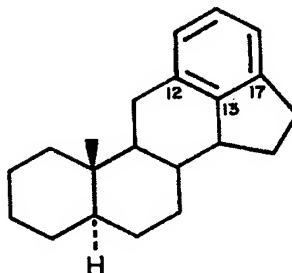
3'*H*-Cyclopropa[2,3]-5 $\alpha$ -androstane



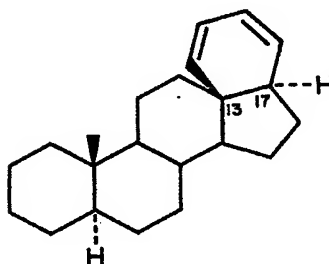
2 $\alpha$ ,3 $\alpha$ -Dihydro-3'*H*-cyclopropa[2,3]-5 $\alpha$ -androstane



17 $\alpha$ *H*-Benzo[12,13,17]-5 $\alpha$ -androstane



(110)  
Benzo[12,13,17]-18-nor-5 $\alpha$ -androstane



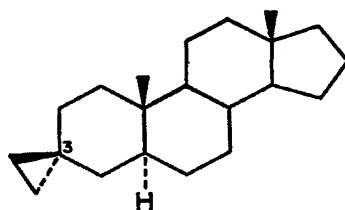
(111)  
17 $\alpha$ H-Benzo[13,17]-18-nor-5 $\alpha$ -androstane

*Note* As shown by examples 108 and 110, insertion of the maximum number of non-cumulative double bonds into the attached component is considered to take place after fusion.

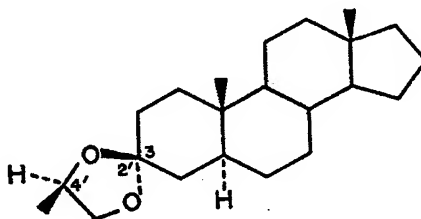
### 3S-10.3. Spiro union with a steroid

Simple spiro systems may be named in an analogous way to bridged steroids (3S-10.1). For example, compound 112 is 3,3-ethylene-5 $\alpha$ -androstane.

In general a spiro union is cited in the normal way (see recommendations A-41.4, B-10.2 in [3]). Examples:



(112)  
Spiro[5 $\alpha$ -androstane-3,1'-cyclopropane]



(113)  
(4'*R*)-4'-Methyl-(3*S*)-spiro[5 $\alpha$ -androstane-3,2'-[1,3]dioxolane]

## REFERENCES

1. IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC) and IUPAC-IUB Commission on Biochemical Nomenclature (CBN). The Nomenclature of Steroids, Revised tentative rules, 1967. *Arch. Biochem. Biophys.* 136, 13-35 (1970), amended 147, 4-7 (1971); *Biochem. J.* 113, 5-28 (1969), amended 127, 613-616 (1972); *Biochemistry*, 8, 2227-2242 (1969), amended 10, 4994-4995 (1971); *Biochim. Biophys. Acta*, 164, 453-486 (1968), amended 248, 387-390 (1971); *Eur. J. Biochem.* 10, 1-19 (1969), amended 25, 1-3 (1972); *Pure Appl. Chem.* 31, 285-322 (1972), with amendments incorporated; also pp. 133-153 of [2], with amendments included.
2. International Union of Biochemistry (1978) *Biochemical nomenclature and related documents*, The Biochemical Society, London.
3. International Union of Pure and Applied Chemistry, *Nomenclature of organic chemistry, Sections A, B, C, D, E, F and H*, 1979 Edition, Pergamon Press, Oxford, 1979. Section E appeared also in pp. 1-18 of [2], and section F in pp. 19-26 of [2] and in *Eur. J. Biochem.* 86, 1-8 (1978).
4. A. Butenandt and L. Poschmann, *Ber. Dtsch. Chem. Ges.* 73, 893-897 (1940); cf. also A. Butenandt, L. Karlson-Poschmann, G. Failer, U. Schiedt and E. Bilkert, *Liebigs Ann. Chem.* 575, 123-144 (1951).
5. IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), Nomenclature of vitamin D. Recommendations 1981. *Arch. Biochem. Biophys.* 218, 342-346 (1982); *Endokrinol. Inform.* 1982(2), 53-62; *Eur. J. Biochem.* 124, 223-227 (1982); *Mol. Cell. Biochem.* 49, 177-181 (1982); *Pure Appl. Chem.* 54, 1511-1516 (1982).
6. *International non-proprietary names (INN) for pharmaceutical substances*, cumulative list 6, World Health Organization, 1982.

## Appendix

## Selected international non-proprietary names (INNs) of steroids

INN	Chemical name	Molecular formula
Acrihellin	5,14-dihydroxy-3 $\beta$ -[(3-methylcrotonoyl)oxy]-19-oxo-5 $\beta$ -bufa-20,22-dienolide	C <sub>29</sub> H <sub>38</sub> O <sub>7</sub>
Actodigin	3 $\beta$ -( $\beta$ -D-glucopyranosyloxy)-14-hydroxy-24-nor-5 $\beta$ ,14 $\beta$ -chol-20(22)-eno-21,23-lactone	C <sub>29</sub> H <sub>44</sub> O <sub>9</sub>
Alfacalcidol	(5Z,7E)-(1S,3R)-9,10-seccholesta-5,7,10(19)-triene-1,3-diol	C <sub>27</sub> H <sub>44</sub> O <sub>2</sub>
Betamethasone	9-fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione	C <sub>22</sub> H <sub>29</sub> FO <sub>5</sub>
Canrenone	3-oxo-17 $\alpha$ -pregna-4,6-diene-21,17-carbolactone	C <sub>22</sub> H <sub>28</sub> O <sub>3</sub>
Clomegestone	6-chloro-17-hydroxy-16 $\alpha$ -methylpregna-4,6-diene-3,20-dione	C <sub>22</sub> H <sub>29</sub> ClO <sub>3</sub>
Cypoterone	6-chloro-1 $\beta$ ,2 $\beta$ -dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-4,6-diene-3,20-dione	C <sub>22</sub> H <sub>27</sub> ClO <sub>3</sub>
Dexamethasone	9-fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione	C <sub>22</sub> H <sub>29</sub> FO <sub>5</sub>
Disogluside	(25R)-3 $\beta$ -( $\beta$ -D-glucopyranosyloxy)spirost-5-ene	C <sub>33</sub> H <sub>52</sub> O <sub>8</sub>
Ethinylestradiol	19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol	C <sub>20</sub> H <sub>24</sub> O <sub>2</sub>
Fluazacort	21-acetoxy-9-fluoro-11 $\beta$ -hydroxy-2'-methyl-16 $\beta$ H-oxazolo-[5',4':16,17]pregna-1,4-diene-3,20-dione	C <sub>25</sub> H <sub>30</sub> FNO <sub>6</sub>
Fluocortin	6 $\alpha$ -fluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3,20-dioxopregna-1,4-dien-21-oic acid	C <sub>22</sub> H <sub>27</sub> FO <sub>5</sub>
Fusidic Acid	(17Z)-ent-16 $\alpha$ -acetoxy-3 $\beta$ ,11 $\beta$ -dihydroxy-4 $\beta$ ,8,14-trimethyl-18-nor-5 $\beta$ ,10 $\alpha$ -cholesta-17(20),24-dien-21-oic acid	C <sub>31</sub> H <sub>48</sub> O <sub>6</sub>
Gestrinone	17-hydroxy-18 $\alpha$ -homo-19-nor-17 $\alpha$ -pregna-4,9,11-trien-20-yn-3-one	C <sub>21</sub> H <sub>24</sub> O <sub>2</sub>
Halometasone	2-chloro-6 $\alpha$ ,9-difluoro-11 $\beta$ ,17,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione	C <sub>22</sub> H <sub>27</sub> ClF <sub>2</sub> O <sub>5</sub>
Hydrocortisone	11 $\beta$ ,17,21-trihydroxypregn-4-ene-3,20-dione	C <sub>21</sub> H <sub>30</sub> O <sub>5</sub>
Mebolazine	17 $\beta$ -hydroxy-2 $\alpha$ ,17-dimethyl-5 $\alpha$ -androstan-3-one azine	C <sub>22</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub>
Medroxyprogesterone	17-hydroxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione	C <sub>22</sub> H <sub>32</sub> O <sub>3</sub>
Meproscillarlin	3 $\beta$ -(6-deoxy-4-O-methyl- $\alpha$ -L-mannopyranosyloxy)-14-hydroxybufa-4,20,22-trienolide	C <sub>31</sub> H <sub>44</sub> O <sub>8</sub>
Mesprenone	7 $\alpha$ -acetylthio-15 $\alpha$ ,16 $\alpha$ -dihydro-3-oxo-3'H-cyclopropa[15,16]-17 $\alpha$ -pregna-1,4-diene-21,17-carbolactone	C <sub>25</sub> H <sub>30</sub> O <sub>4</sub> S
Mestranol	3-methoxy-19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yn-17-ol	C <sub>21</sub> H <sub>26</sub> O <sub>2</sub>
Naflocort	9-fluoro-1',4'-dihydro-11 $\beta$ ,21-dihydroxy-16 $\beta$ H-naphtho[2',3':16,17]-pregna-1,4-diene-3,20-dione	C <sub>29</sub> H <sub>33</sub> FO <sub>4</sub>
Norethisterone	17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one	C <sub>20</sub> H <sub>26</sub> O <sub>2</sub>
Norgesterone	17-hydroxy-19-nor-17 $\alpha$ -pregna-5(10),20-dien-3-one	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>
Norgestrel	rac-17-hydroxy-18 $\alpha$ -homo-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one	C <sub>21</sub> H <sub>28</sub> O <sub>2</sub>
Oxandrolone	17 $\beta$ -hydroxy-17 $\alpha$ -methyl-2-oxa-5 $\alpha$ -androstan-3-one	C <sub>19</sub> H <sub>30</sub> O <sub>3</sub>
Oxymetholone	17 $\beta$ -hydroxy-2-(hydroxymethylene)-17 $\alpha$ -methyl-5 $\alpha$ -androstan-3-one	C <sub>19</sub> H <sub>28</sub> O <sub>3</sub>
Pancuronium bromide	1,1'-(3 $\alpha$ ,17 $\beta$ -diacetoxy-5 $\alpha$ -androstan-2 $\beta$ ,16 $\beta$ -diyl)bis(1-methylpiperidinium) dibromide	C <sub>35</sub> H <sub>60</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub>
Prednisolone	11 $\beta$ ,17,21-trihydroxypregna-1,4-diene-3,20-dione	C <sub>21</sub> H <sub>28</sub> O <sub>5</sub>
Prednisone	17,21-dihydroxypregna-1,4-diene-3,11,20-trione	C <sub>21</sub> H <sub>26</sub> O <sub>5</sub>
Proscillarlin	3 $\beta$ -(6-deoxy- $\alpha$ -L-mannopyranosyloxy)-14-hydroxybufa-4,20,22-trienolide	C <sub>30</sub> H <sub>42</sub> O <sub>8</sub>
Roxibolone	11 $\beta$ ,17 $\beta$ -dihydroxy-17 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-2-carboxylic acid	C <sub>21</sub> H <sub>28</sub> O <sub>5</sub>
Spirolactone	7 $\alpha$ -acetylthio-3-oxo-17 $\alpha$ -pregn-4-ene-21,17-carbolactone	C <sub>24</sub> H <sub>32</sub> O <sub>4</sub> S
Timobesone	5-methyl 9-fluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\beta$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate	C <sub>22</sub> H <sub>29</sub> FO <sub>4</sub> S
Triamcinolone	9-fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione	C <sub>21</sub> H <sub>27</sub> FO <sub>6</sub>
Ursodeoxycholic acid	3 $\alpha$ ,7 $\beta$ -dihydroxy-5 $\beta$ -cholan-24-oic acid	C <sub>24</sub> H <sub>40</sub> O <sub>4</sub>

# Selective Homogeneous Hydrogenation of 3-Oxo-1,4-diene Steroids. III.<sup>1)</sup> On the Formation of Saturated 5 $\alpha$ -Ketone in the Hydrogenation Catalyzed by Dichlorotris(triphenylphosphine)ruthenium

Shigeo NISHIMURA, Tomio ICHINO, Akira AKIMOTO, Kiyoshi TSUNEDA,\* and Hiromu MORI\*

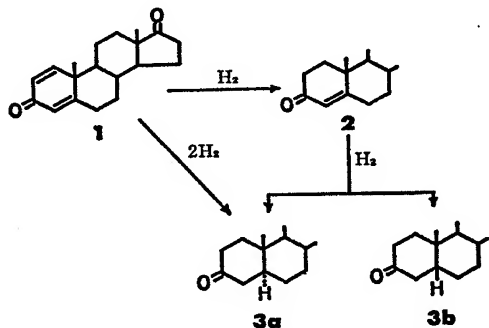
Department of Industrial Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184

\*Chemical Research Laboratory, Teikoku Hormone Manufacturing Co., Ltd., Shimosakunobe, Kawasaki 213

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Hydrogenation of 1,4-androstadiene-2,17-dione (**1**) with  $\text{RuCl}_2(\text{Ph}_3\text{P})_3$  gives some saturated 5 $\alpha$ -ketone together with 4-androstene-3,17-dione (**2**). The ratio of **2** to the saturated ketone formed increases almost in proportion to hydrogen pressure. The rate dependence upon hydrogen pressure has been shown to be first-order for formation of **2** and zero-order for formation of the saturated ketone. A mechanism which involves a 1,5-hydride shift at an intermediate species is proposed for the stereoselective formation of the 5 $\alpha$ -ketone.

In previous papers,<sup>1,2)</sup> it was shown that 1,4-androstadiene-3,17-dione (**1**) is hydrogenated selectively to 4-androstene-3,17-dione (**2**) with dichlorotris(triarylphosphine)rutheniums as catalysts. Although hydrogenation of **2** to saturated ketones (**3a** and **3b**) was very slow with the ruthenium complex some saturated 5 $\alpha$ -ketone was found to arise directly from **1**.<sup>2)</sup> This was in contrast to the hydrogenation catalyzed by chlorotris(triphenylphosphine)rhodium<sup>3,4)</sup> where saturated ketones were all produced consecutively through **2**.<sup>2)</sup>



Scheme 1. Hydrogenation pathways of 1,4-androstadiene-3,17-dione (**1**).

This paper describes further studies which were undertaken to get an insight into the mechanism of formation of the saturated 5 $\alpha$ -ketone in the ruthenium complex catalyzed hydrogenation.

## Experimental

**Material.** 1,4-Androstadiene-3,17-dione (**1**) was obtained from the Kikkoman Shoyu Co. and used without further purification, mp 138—139 °C.

**Catalyst.** Dichlorotris(triphenylphosphine)ruthenium was prepared as described previously.<sup>1)</sup>

**Hydrogenation and Analysis of the Products.** The hydrogenation apparatus and the method of analysis of the products were the same as those described previously.<sup>1)</sup> **1** (500 mg) was hydrogenated with 50 mg of the ruthenium complex in 10 ml benzene at 50 °C under various hydrogen pressures. During each hydrogenation the hydrogen pressure was kept almost constant. The reaction time was varied from 505 min for the hydrogenation at the lowest pressure (2.2 kg/cm<sup>2</sup>)

to 60 min for that at the highest pressure (101 kg/cm<sup>2</sup>). The conversion of **1** ranged from 16% to 42% by hydrogenations. The pseudo-first-order rate constants were calculated from the compositions of reaction mixtures employing the integrated form of Eq. (1).

## Results

Figure 1 shows the effect of hydrogen pressure on the ratio of **2** to saturated ketone formed in the hydrogenation of **1** in benzene at 50 °C. Hydrogenation of **2** to saturated ketones **3a** and **3b** was extremely slow under these conditions and this ratio was, therefore, practically independent of the conversion of **1** at a given hydrogen pressure. As described previously,<sup>2)</sup> the saturated ketone formed here is predominantly 5 $\alpha$ -androstane-3,17-dione (**3a**) and this is also indicative that the saturated ketone was not formed through **2**, because hydrogenation of **2** gave an about 2 : 1 mixture of **3a** and **3b**. As is seen from Fig. 1, the ratio of **2** to the saturated ketone increases

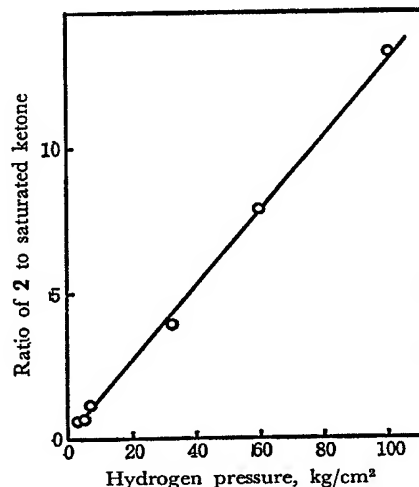


Fig. 1. Effect of hydrogen pressure on the ratio of 4-androstene-3,17-dione (**2**) to the saturated ketone formed in the hydrogenation of **1**. **1** (500 mg) was hydrogenated with 50 mg of  $\text{RuCl}_2(\text{Ph}_3\text{P})_3$  in 10 ml benzene at 50 °C. Each hydrogenation was performed at nearly constant pressure.

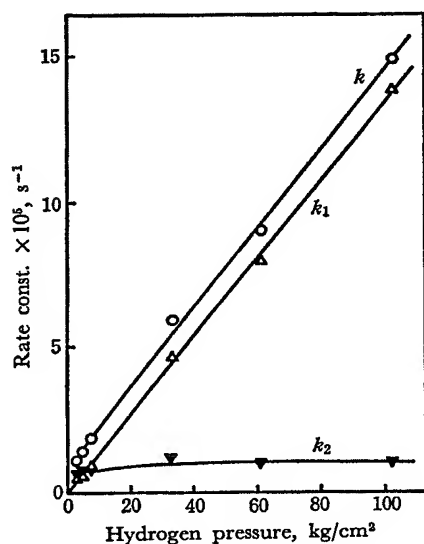


Fig. 2. Effects of hydrogen pressure on the conversion of **1**, the formation of **2** and the formation of saturated ketone.  $k$ ,  $k_1$ , and  $k_2$  are pseudo-first-order rate constants defined by Eq. (1). For experimental conditions, see the footnote of Fig. 1.

almost in proportion to the hydrogen pressure in a wide range of 2 to more than 100 kg/cm<sup>2</sup>.

Figure 2 shows the effect of hydrogen pressure on a pseudo-first-order rate constant  $k$  defined by Eq. (1).<sup>5</sup> The rate constant  $k$  can be separated into the

$$-\frac{d[1]}{dt} = k[1] = (k_1 + k_2)[1] \quad (1)$$

two rate constants  $k_1$  and  $k_2$  for formation of **2** and the saturated ketone, respectively, from the results shown in Fig. 1. From the effects of hydrogen pressure on  $k_1$  and  $k_2$  thus obtained (Fig. 2), it is concluded that the rate of formation of **2** is first-order in hydrogen pressure while that of the saturated ketone is independent of hydrogen pressure. At low pressures, however,  $k_2$  appears to decrease with decreasing hydrogen pressure.

From the plots of the log of the ratio 2: saturated ketone vs. the reciprocal of reaction temperature

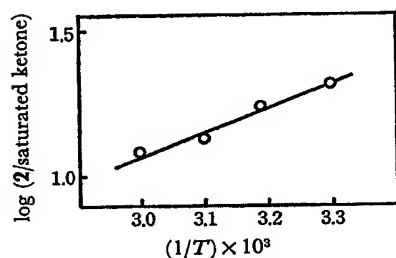
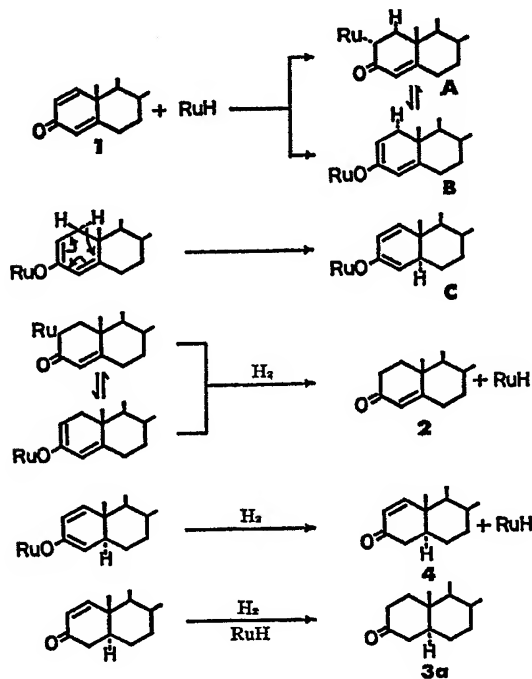


Fig. 3. Effect of reaction temperature on the ratio of **2** to the saturated ketone formed in the hydrogenation of **1**. **1** (500 mg) was hydrogenated with 50 mg of RuCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>3</sub> in 10 ml benzene at 100 kg/cm<sup>2</sup> hydrogen pressure.

(Fig. 3), we know that the apparent activation energy for formation of saturated ketone is 3.8 kcal/mol higher than for formation of **2**. Thus a better selectivity for **2** is obtained in the hydrogenation at a low temperature.

### Discussion

The active species in the hydrogenation catalyzed by dichlorotris(triphenylphosphine)ruthenium is considered to be the hydrido complex RuClH(Ph<sub>3</sub>P)<sub>3</sub> formed by the hydrogenolysis of the dichloro complex.<sup>6,7</sup> The first step of the hydrogenation of **1**, therefore, will be the addition of the hydrido complex (abbreviated as RuH) to **1**, probably from the  $\alpha$ -face.<sup>4</sup> Although the mode of addition of RuH to an  $\alpha,\beta$ -unsaturated ketone is not certain, it might be presumed to occur in the following ways: 1,2 to the C<sub>1</sub>-C<sub>2</sub> double bond to give **A** or 1,4 to give **B** as shown in Scheme 2.<sup>8</sup> If we assume that isomerization of **B** to **C** by a 1,5-hydride shift at the cyclic conjugated diene system would occur during the hydrogenation of **A** or **B**,<sup>9</sup> the stereoselective formation of saturated 5 $\alpha$ -ketone **3a** could be accounted for because such hydride shifts would be expected to occur without difficulty between quasi-axial 1 $\alpha$  and axial 5 $\alpha$  positions, assisted by the cyclic conjugated system.<sup>10</sup> The observed zero-order dependence of the rate of formation of **3a** upon hydrogen pressure will not be in conflict with this mechanism if we assume that the hydride shift is rate-controlling in the course of hydrogenation leading to the formation of **3a**. The driving



Scheme 2. A mechanism for formation of 4-androstene-3,17-dione (**2**) and saturated 5 $\alpha$ -ketone (**3a**) in the ruthenium complex catalyzed hydrogenation of 1,4-androstadiene-3,17-dione (**1**).

force for the isomerization of **B** is presumed to be the decrease of electron density at the C-5 carbon atom, which would be caused by the coordination of the enolate anion to ruthenium.<sup>11)</sup> The hydrogen chloride liberated by the hydrogenolysis of the dichloro ruthenium complex may contribute to this decrease of electron density by interacting with the triphenylphosphine ligand. The effect of the addition of triethylamine to depress the formation of the saturated ketone<sup>1)</sup> may give a support for this consideration, because the degree of the depression caused by the addition of triethylamine was so great (from 10.5% to 1.7%), and such a great effect would be difficult to explain by an only twofold increase in the rate of hydrogenation with addition of the amine alone.

From the observed dependencies of the rates on hydrogen pressure, it seems that **C** and **4** are hydrogenated faster than those species which afford **2** on hydrogenation. It is suggested that **C** and **4**, which both have the 5 $\alpha$  configuration, will be less hindered than **A** and **B** for the hydrogenation from the  $\alpha$ -face, because the 5 $\alpha$  species are in a flatter conformation regarding the rings A and B than the  $\Delta^4$  species such as **A** and **B**. This is supported by the fact that 5 $\alpha$ -1-androstene-3,17-dione (**4**) is hydrogenated more easily than **1** with the ruthenium complex under comparable conditions.<sup>12)</sup>

The authors are grateful to Professor J. A. Marshall of Northwestern University for his valuable suggestion concerning the 1,5-hydride shift.

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- 9) For the preference of 1,5- over 1,3-hydrogen shift, see R. T. Morrison and R. N. Boyd, "Organic Chemistry," 3rd ed., Allyn and Bacon, Inc., New York (1973), p. 954.
- 10) The saturated 5 $\alpha$ -ketone formed in the deuteration of **1** at about 40% conversion, on treatment with methanolic sodium hydroxide, gave 5 $\alpha$ -ketone- $d_2$  as the predominant product. This result suggests that no exchange occurred at the C-6 carbon during the deuteration and excludes the mechanism involving the C-6 hydrogen, e.g., enolization of **1** prior to hydrogenation, which may well explain the stereospecific 5 $\alpha$ -ketone formation.
- 11) For a coordination of a similar type, see H. W. Thompson and E. McPherson, *J. Amer. Chem. Soc.*, **96**, 6232 (1974).
- 12) **4** was completely hydrogenated to **3a**, compared with only 84% conversion of **1** under the same conditions (unpublished results; see also Ref. 2)